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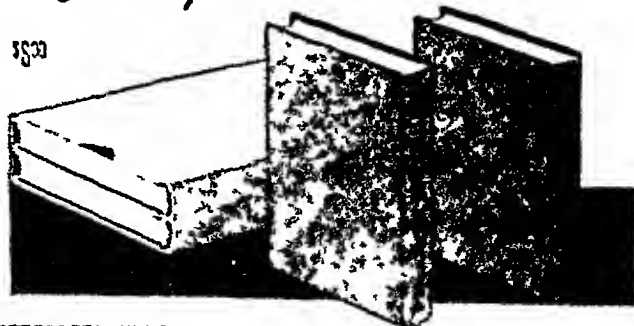
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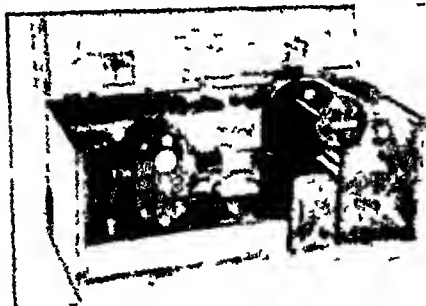
By Roy M. Dorcus, Associate Professor of Psychology, University of California at Los Angeles, and G. Wilson Shaffer, Dean of the College of Arts and Sciences, Lecturer in Psychology, Professor of Health and Physical Education, Johns Hopkins University. Psychologist, Sheppard-Pratt Hospital, Towson, Md. Third edition (1945) over 500 pages, illustrated. \$1.00. Ready March 1.

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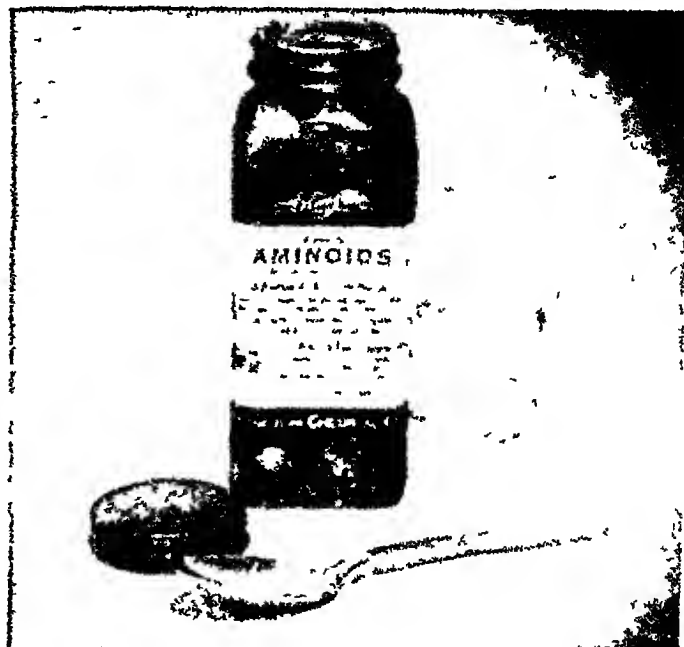
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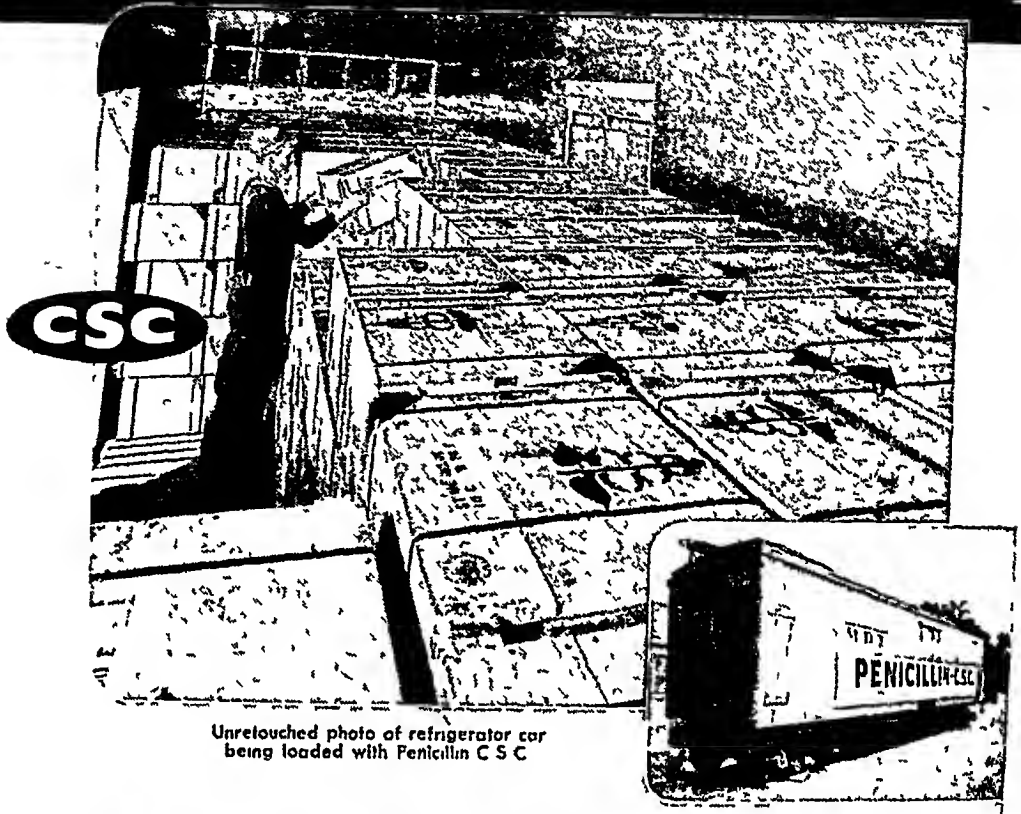
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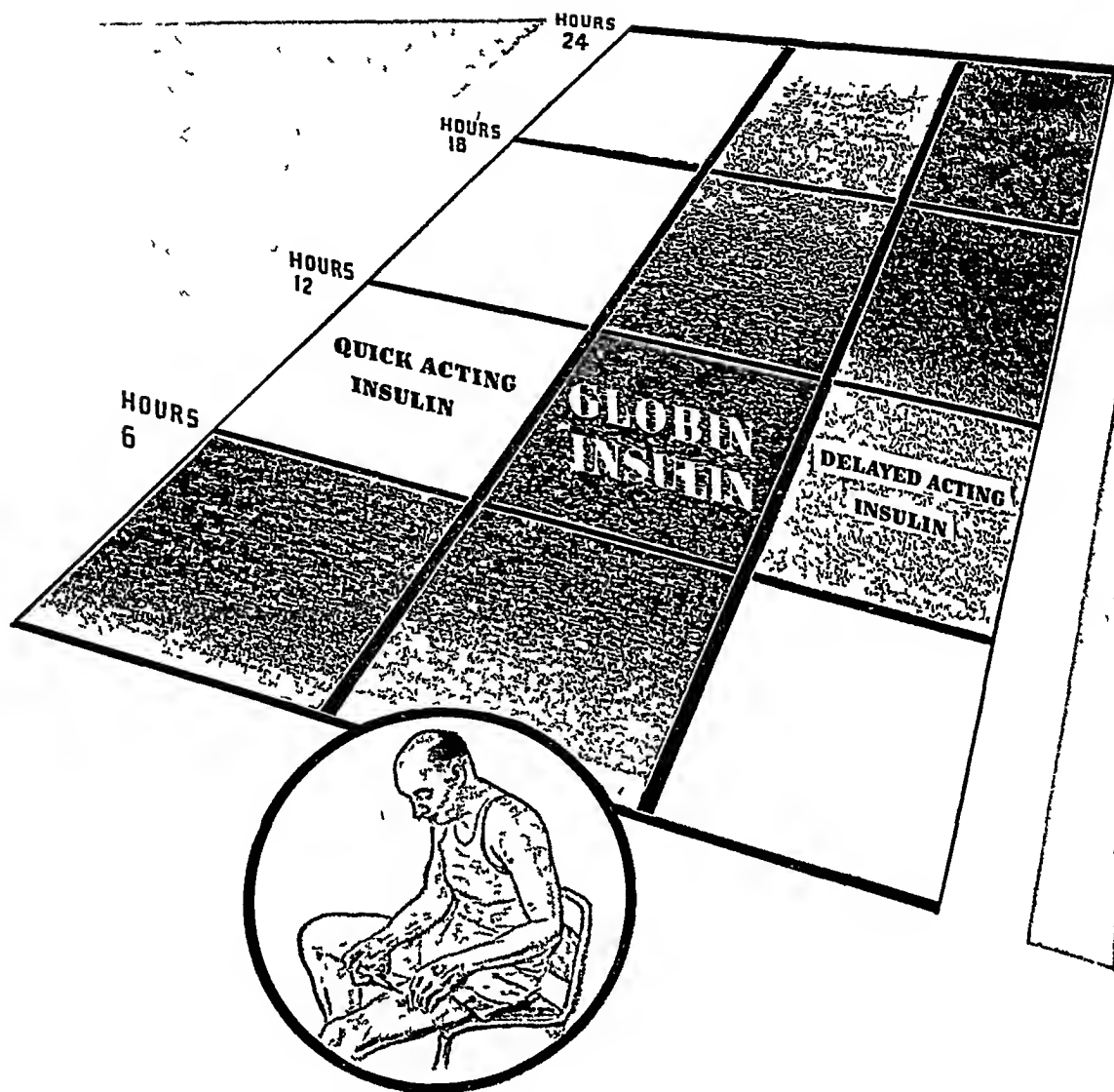
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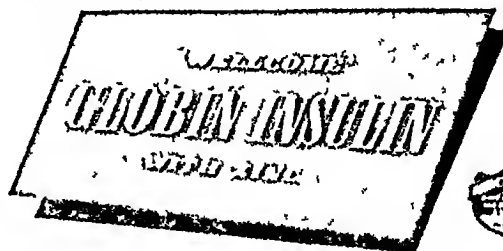
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\*Burke B.S., Heding A.V. and Smith H.C. "Nutrition Studies During Pregnancy," J. Ped. 27: 506-515 (Nov.) 1943

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*J. A. Otolaryng.* 33:109, 124, 1874

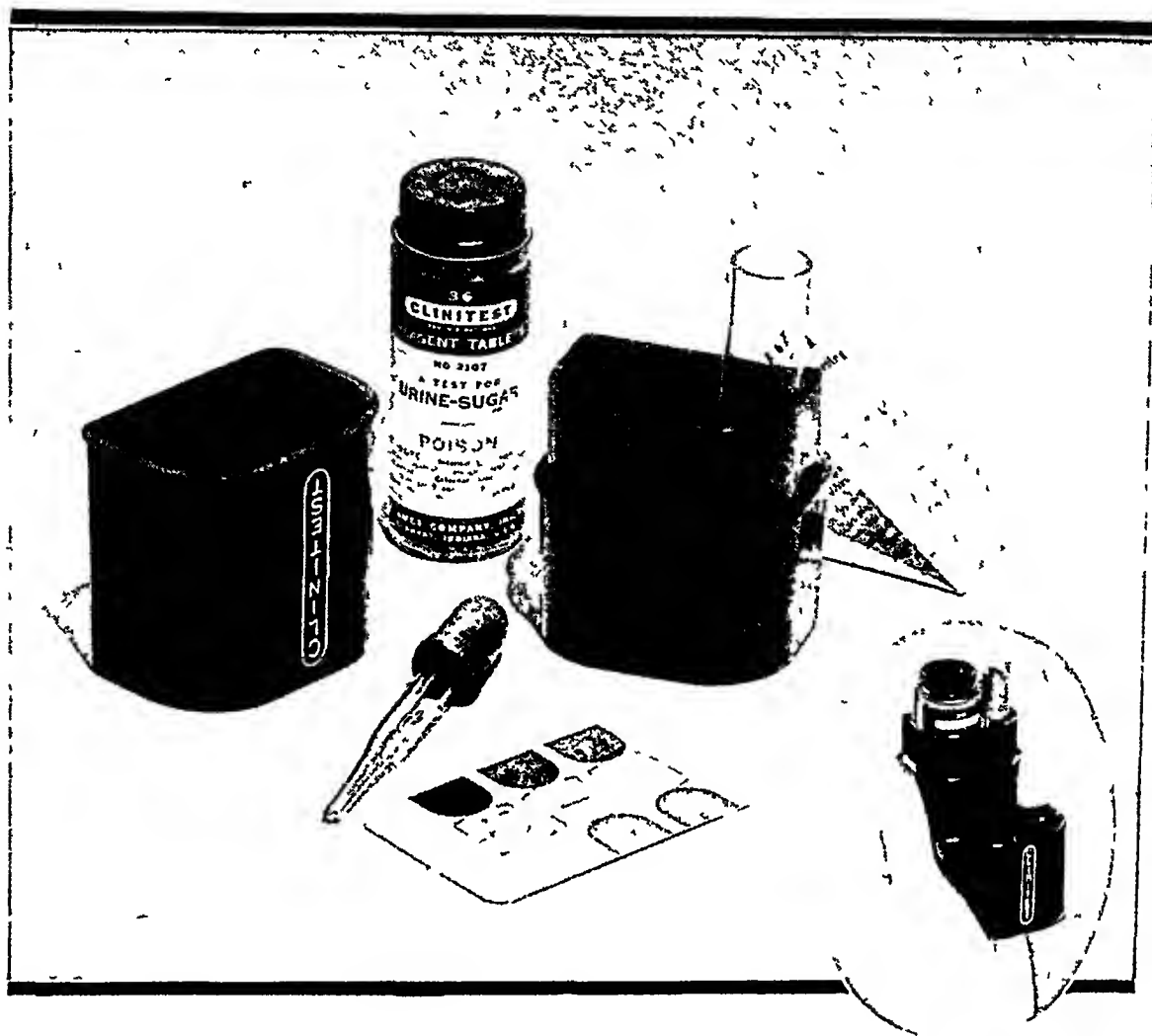


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\*Gray, H. and Tainter, M. L., *Am. J. Dig. Dis.* 8:130, 1941

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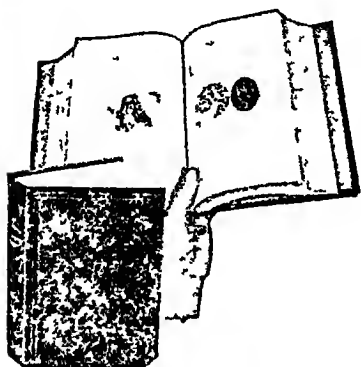
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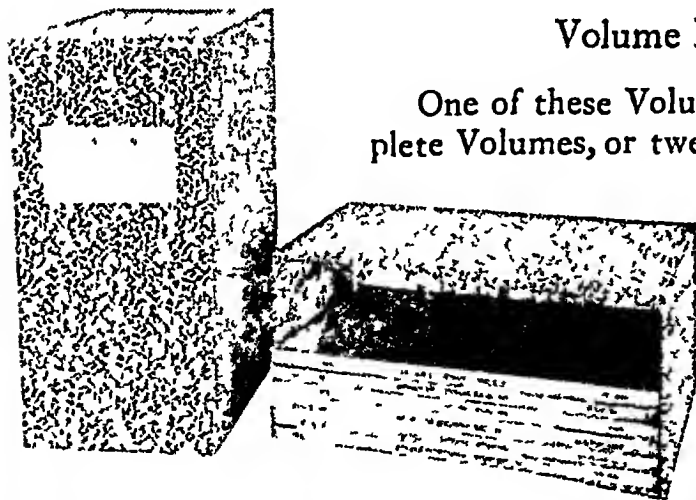
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d Aspartic Acid		N 10.4%—10.6%	N 10.52%
Beta-Alanine		N 15.6%—15.8%	N 15.72%
d Alpha-Alanine		N 15.6%—15.8%	N 15.72%
l (+) Cysteine Hydrochloride	(not less than 98% on the anhydrous basis)		
l (—) Cystine	$[\alpha]_D^{30}$ —200° to —203°	S 26.3%—27%	S 26.69%
l (+) Glutamic Acid	$[\alpha]_D^{25}$ in normal HCl: +30.7° to +32.5°	N 9.4%—9.6%	N 9.52%
d Glutamic Acid Monohydrate		N (in anhydr.) 9.4%—9.6%	N 9.52%
l (+) Histidine Monohydrochloride	$[\alpha]_D^{25}$ (anhy. basis in normal HCl): +9.5° to +11°	N (in anhydr.) 21.7%—22.0%	N 21.93%
l (—) Hydroxyproline	$[\alpha]_D^{25}$ —75.5° to —76.5°	N 10.6%—10.8%	N 10.68%
d Isoleucine		N 10.5%—10.8%	N 10.68%
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* l (—) Leucine	$[\alpha]_D^{25}$ (in 20% HCl): +15° to +16.2°	N 10.5%—10.8%	N 10.68%
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d Lysine Monohydrochloride		N 15.2%—15.4%	N 15.34%
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		S 21.3%—21.6%	S 21.5%
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d Threonine		N 11.6%—11.9%	N 11.76%
d Tryptophane		N 13.5%—13.8%	N 13.75%
* l (—) Tryptophane	$[\alpha]_D^{25}$ —31.5° to —33°	N 13.5%—13.8%	N 13.75%
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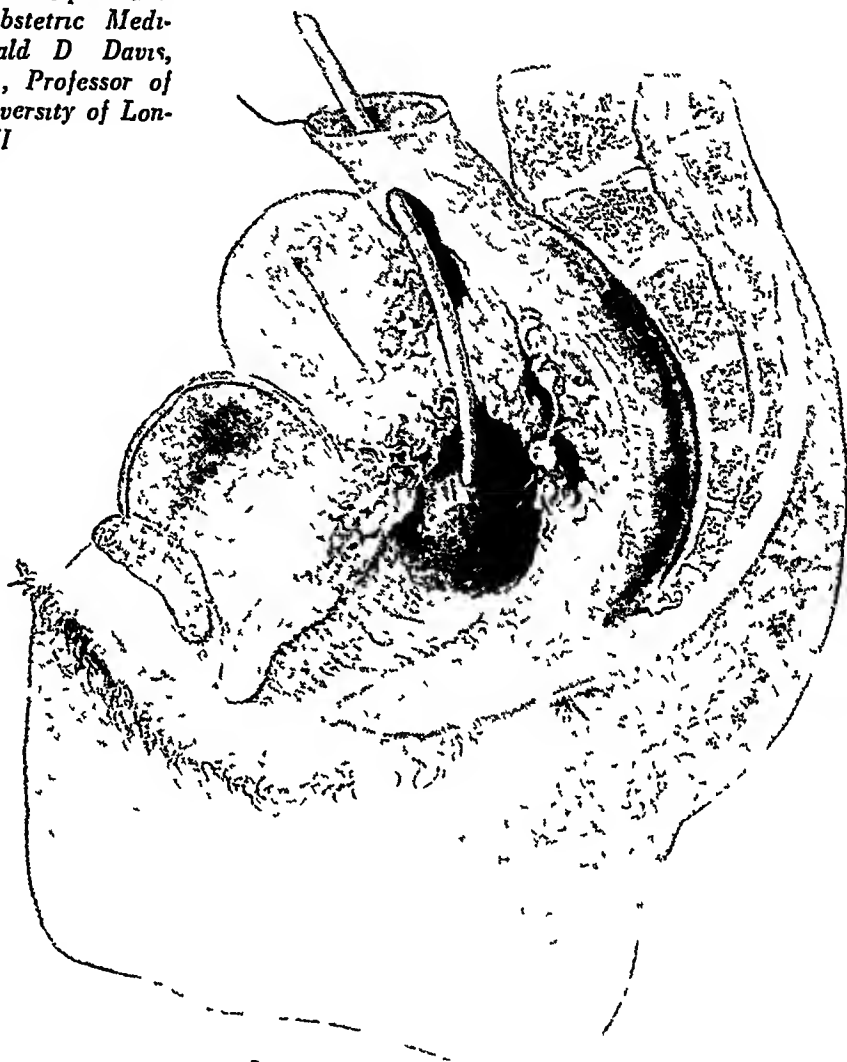


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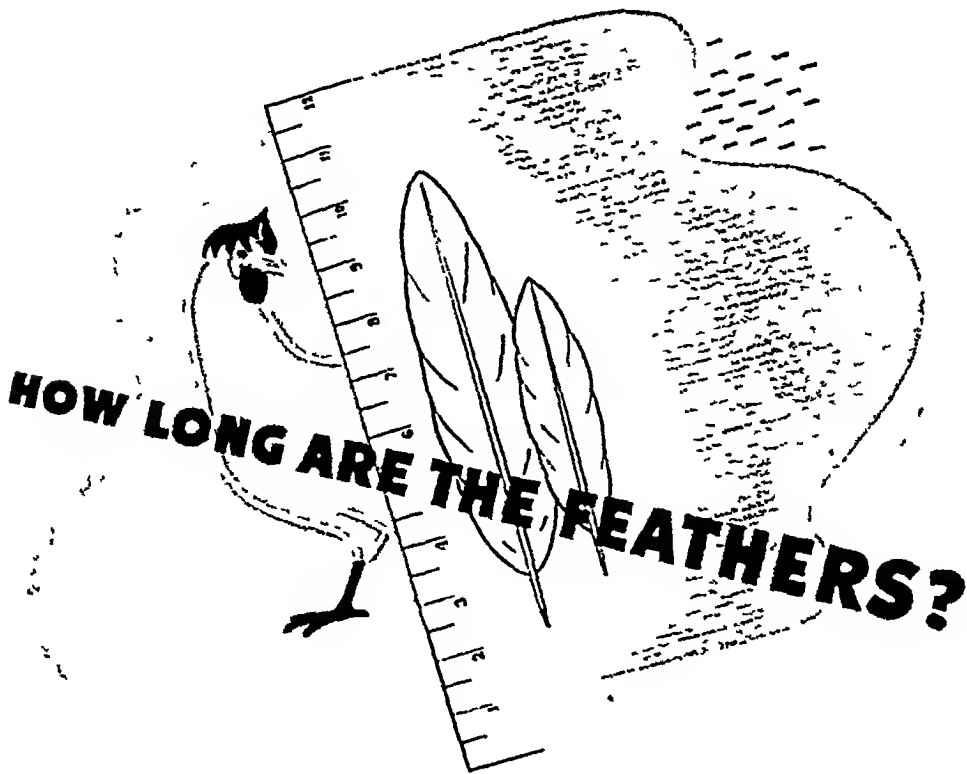
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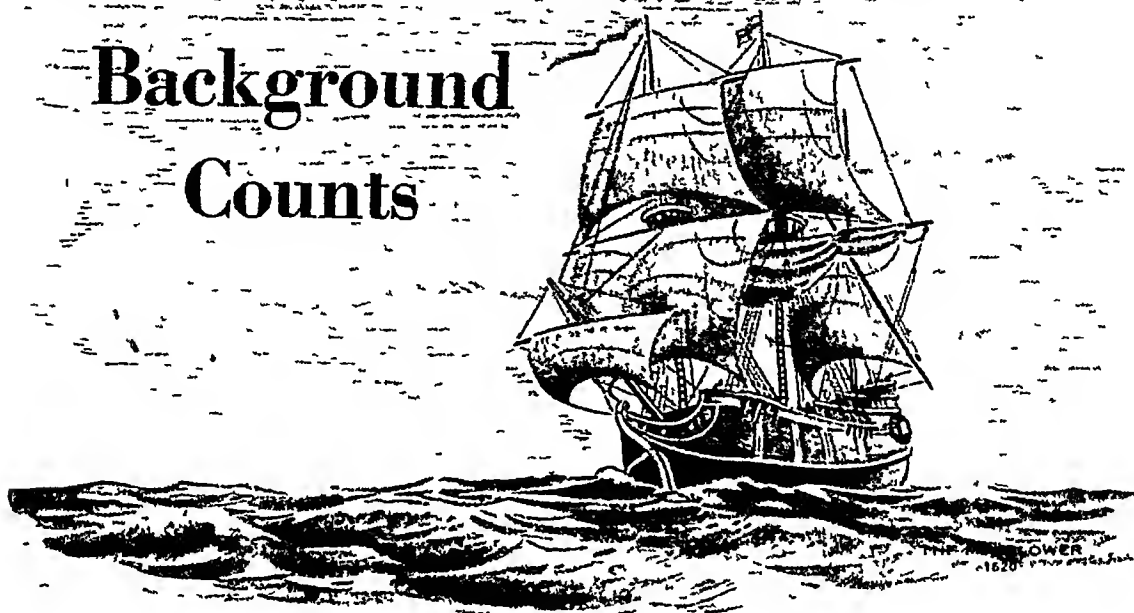
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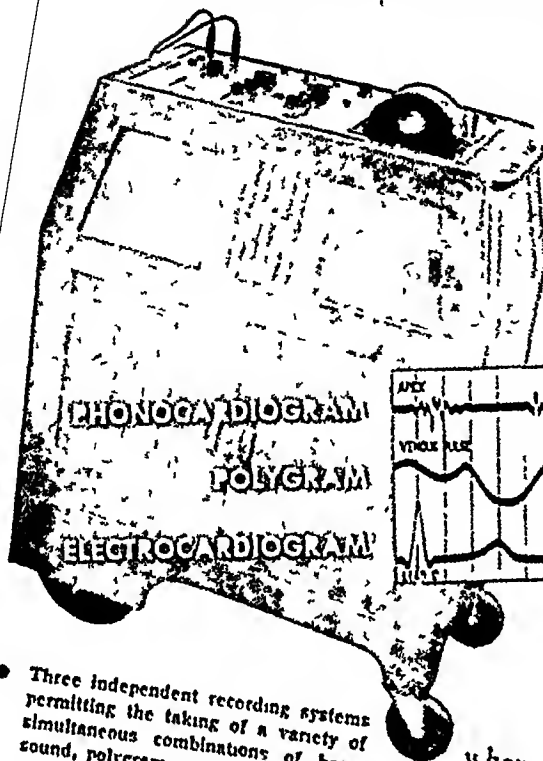
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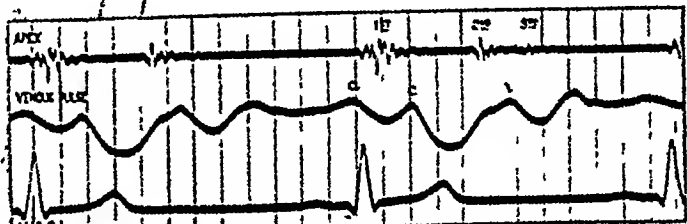
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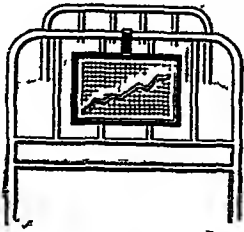
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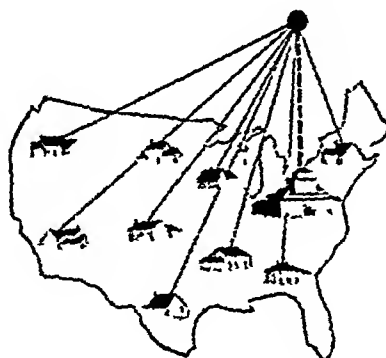
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1 Tracy Putnam: Convulsive Seizures, p. 4. J. B. Lippincott Co. 1942.

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# ANNALS OF INTERNAL MEDICINE

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## THE EPIDEMIOLOGY OF ACUTE RESPIRATORY INFECTIONS CONDITIONED BY SULFONAMIDES.

### I. GENERAL CLINICAL CONSIDERATIONS \*

By MORRIS SIEGEL and L. A. JULIANELLI, *New York, N. Y.*

ALTHOUGH an impressive proportion of public health problems associated with prevention of disease has been solved in a gratifying manner, it must be admitted that in the case of respiratory infections as a class prophylaxis remains to be accomplished. Withstanding the attempts made in the past with prophylactic immunization, spraying preparations, personal hygiene, isolation, and, to a limited extent, ultraviolet radiation and aerosols, the still resistant examples of this group of diseases apparently must be controlled by newer methods of approach. It was reflected in this connection that by virtue of their bacteriostatic action, sulfonamides might be of value in certain instances in attaining the desired objective. Even in instances of virus infection (e.g., common cold, influenza, atypical pneumonia) it was reasoned that benefit might be achieved because of the retarding influence of the drugs on the growth of those organisms most commonly implicated in secondary complications, even though the primary or viral agent is itself unaffected. That such predication might actually be the case was indicated by preliminary studies already published from this laboratory.<sup>1, 2</sup> Thus, it was revealed that prompt prescription of sulfadiazine at the onset of acute symptoms of the upper air passages was followed in certain cases by a decrease in the severity and duration of complications. Favorable clinical effects attributable to sulfadiazine were ascribed to the inhibitory behavior of the drug on susceptible, offending organisms.

During the fall and winter of 1942-1943, a more elaborate study was undertaken of the value of sulfadiazine in the control of the more common

\* Received for publication March 11, 1944.

acute respiratory infections. The investigation was conducted over an extended period in a closed population at Letchworth Village,<sup>3</sup> a state (New York) institution for the feebleminded. Both clinical and bacteriological observations were made, but in the present communication only the former will be reported.

### METHOD OF STUDY

*1 Subjects under study* The individuals utilized in the survey were inmates of a single cottage (Iota) in the institution. The cottage accommodated 130 children of the lowest mental rating, who by past experience proved to be particularly susceptible to both acute respiratory infection and secondary bacterial complications. The ages varied from two to 15 years, with the average about eight years. Some 25 of the youngest subjects were housed in a nursery, while the remainder slept in two dormitories containing 50 to 60 beds spaced only several inches apart and arranged in three rows at intervals of about three feet. Excluding those in the nursery, the children were allowed to intermingle in the cottage without restriction so that contact was close and intimate. Their activity was limited and consisted almost entirely of sitting or aimless wandering within the confines of the cottage and an adjoining outdoor porch. Although association with the inmates of other cottages was confined entirely to necessary visits to clinic or hospital, contact with individuals other than those residing in Iota cottage came through employees, inmate-workers, visitors (usually on Sundays and holidays), and new admissions who replaced withdrawals at the average rate of one or two a week. Of the 130 children, 60 were selected for study. In alternate order of admission, 30 were allocated to a group receiving sulfadiazine ("treated group") and 30, to a control or "untreated" group.

About 88 per cent of the children in the study were white and 12 per cent colored. The duration of residence at the institution varied from three months to seven years, about 53 per cent had been in the cottage for two or more years, 27 per cent for one year, and 20 per cent for less than a year. Their ages varied from four to 14 years, the average being 7.5 years for the treated and 7.7 years for the controls. Their weights ranged from 32 to 88 pounds, with about 55 per cent fluctuating between 40 and 60 pounds. The average weights were 46.8 pounds for the treated and 48.7 pounds for the controls. The frequency of mongolism was high, attaining a rate of about 23 per cent.

Comparative data on the number of acute respiratory infections observed in the two groups during the year preceding the study are summarized below. The infections listed occurred entirely during the period of the previous year corresponding to that of the present year's study. During 1941-1942, the year preceding the test period, 100 colds were observed among the children in the study, 49 in the treated group and 51 among the controls. During the same interval three of the children in each group had lobar pneu-

Colds per child during year preceding test period (Dec 1941-Mar 1942)	Treated group		Control group	
	Children	Colds	Children	Colds
0	9	0	11	0
1	7	7	8	8
2	6	12	1	2
3	5	15	4	12
4	1	4	2	8
5	1	5	3	15
6	1	6	1	6
Total	30	49	30	51

pneumonia due presumably to *Pneumococcus* types I, V, VI, VII, XIV, and XXII.

The foregoing data reveal that the two groups selected for study were similar in respect to physical development, mental characteristics, duration of residence at the institution, and incidence of endemic respiratory infections including pneumonia.

2 *Administration of drug* Sulfadiazine\* was used daily in the treated group from December 11, 1942 to March 25, 1943, a period of 15 weeks ("test period" or "period of drug therapy"). During the first two months (December 11 to February 10) one gram (2 tablets) of the drug was given daily in three divided doses as follows: 0.25 gram ( $\frac{1}{2}$  tablet) at 6 a.m. with breakfast, 0.25 gram ( $\frac{1}{2}$  tablet) at 11 a.m. with lunch, and 0.5 gram (1 tablet) at 6 p.m. with an egg-nog. After February 10, the daily dosage was doubled to two grams, given in four equally divided portions of 0.50 gram (1 tablet) at 6 a.m. with breakfast, 11 a.m. with lunch, 4 p.m. with dinner, and 8 p.m. with an egg-nog. This method of administration was maintained for a period of six weeks, from February 11 to March 25. Within the entire period of daily drug therapy, then, each treated child received a total of 148 grams of sulfadiazine. After March 25, the drug was used only in the event of acute respiratory infection, and then for seven days: two grams daily for the first four days and one gram daily for the last three days. Only those in the treated group received sulfadiazine; except for the use of the drug, the controls were managed as were the treated children.

During the period of drug therapy all the children were ambulatory and permitted their usual activities within the cottage. When ill they were confined to bed within their dormitory and treated in the routine manner which called for in children on the first day: a light diet and increased amounts of fluids during the acute stage and acetylsalicylic acid if needed. In addition, the treated children received sulfadiazine in minimum doses of two grams daily for the first four days of illness and after that, the usual daily dose prescribed in the study. Those who developed pneumonia or became very ill for any reason were transferred to the hospital maintained at the institution.

There they were treated in an open ward of 50 beds for one or more days until they were considered well enough to return to the cottage

3 *Collateral laboratory examinations* During the period of daily drug therapy, nasopharyngeal cultures were made every seven to 10 days during the period of daily drug therapy, and every 10 days from May 6 to June 14 in the post-therapy period. The details of the methods employed will be described in reports dealing with the bacteriological data

Periodic examinations of the blood and urine were also conducted. Red and white blood cell counts (total and differential) were done at weekly intervals, and hemoglobin was determined at monthly intervals. Analyses for non-protein nitrogen were performed on three occasions during the course of the study. Blood specimens for the determination of free sulfadiazine were obtained every seven to 10 days,\* at the same time that throat smears were made

#### RESULTS FOLLOWING ADMINISTRATION OF SULFADIAZINE

*Effect on the subjects* Before entering into a description of the effects of the drug on respiratory infection and accompanying complications, it is desirable to summarize first the data bearing on the toxicity of sulfadiazine. Each of the treated children received 148 grams of sulfadiazine over a period of 15 weeks and this treatment was followed by little sign of toxic reaction. Thus, a transient rash was encountered in only two children. There was no loss of appetite and no vomiting. The average weight for the treated group increased 15 pounds, as compared with 10 pound in the control group. Although most of the urines examined revealed sulfadiazine crystals estimated at a few to many, with microscopically, a few red blood cells and at times, a trace of albumin, there was no indication of gross bleeding or urinary obstruction. Similarly, none of the bloods revealed important increases in non-protein nitrogen. Furthermore, there was no critical drop in blood count during the period of observation. The red blood cells fluctuated slightly, whereas the average white blood cell count dropped 37 per cent in the treated group and 30 per cent in the control group.

*Blood concentration of sulfadiazine* The amount of free sulfadiazine in the blood varied considerably with each individual. The average blood levels for the different subjects fluctuated from 1.9 to 6.9 milligrams per 100 c.c. when the daily dosage was one gram. With increase of the dosage to two grams daily, there was a corresponding increase in the blood level reaching from 3.2 to 13.9 milligrams per 100 c.c. The average blood level was maintained at 3.4 milligrams per 100 c.c. on a daily dosage of one gram and 7.2 milligrams on a daily dosage of two grams.

*Effect on infections* Contrary to expectations, the incidence of pneumonia and other serious acute respiratory illnesses ran unusually low during

\* During the early part of the study, the blood levels of free sulfadiazine were determined through the courtesy of Dr. Isaac G. M. Bullowa at Harlem Hospital, New York.

the period of study, not only in cottage Iota where the study was conducted, but in the entire institution. In cottage Iota, the differences between the current and past periods were quite marked, as shown in the following tabulation of the number of cases of pneumonia from September through May of each year beginning with 1939.

NUMBER OF CASES OF PNEUMONIA IN COTTAGE IOTA FROM 1939 TO 1943

Month	Past years			Current year
	1939-40	1940-41	1941-42	1942-1943
September	7	0	2	1
October	7	0	3	0
November	3	0	1	0
December	2	0	1	0
January	3	1	4	1
February	8	0	0	1
March	3	7	3	0
April	5	9	0	1
May	3	3	1	1
Total	41	20	15	8

On the basis of past experience in cottage Iota, from eight to 16 cases of pneumonia were anticipated during the test period from December 1942 through March 1943. Instead, only two cases occurred. About a month after the test period, an outbreak of scarlet fever occurred, lasting from April 24 to June 2 and affecting 28 (21.5 per cent) inmates of the cottage. The disease was responsible for three cases of pneumonia during May, as many, in fact, as occurred in the preceding six months.

The relative infrequency of pneumonia during the test period of 1942-1943 was paralleled by a decrease in the incidence and severity of the common acute respiratory infections observed in the cottage. In early December, before drug therapy was begun, there were only few mild instances of acute infections of the respiratory tract, whereas from December 11 to March 25 when sulfadiazine was administered, the number of cases fluctuated considerably. In a general way, they were moderately high during the middle of January and the beginning of March but fairly low at other times. During the entire period, there were no outbreaks either with severe infections or with high attack rate. This was in contradistinction to the outbreaks in the past when usually they occurred at least once or twice each winter. Very few cases were seen toward the end of the test period and for the first two weeks thereafter. Then, the incidence increased markedly during the latter part of April and in May when scarlet fever occurred.

There were no striking clinical differences between the two groups throughout drug therapy. A purulent nasal discharge or other sign of infection of the upper respiratory tract was observed at some time during the test period in 25 treated and 23 control children. The average duration of



the nasal discharge was somewhat longer in the control group than in the treated, but the differences were not great enough to be considered significant in the small numbers observed

Acute febrile respiratory infections were observed in seven of the 30 treated children receiving daily drug therapy. One child had two attacks and the others, single attacks, making a total of eight cases for the group. The infections were clinically limited to the upper respiratory passages. In the control group, there were also seven children with a total of eight acute febrile infections. Seven of the infections were limited to the upper respiratory tract, while the eighth case was further involved with lobar pneumonia of the right lower lobe. In this patient, *Pneumococcus* type XI was isolated from throat smears taken before, during and after the attack. Aside from the one case of lobar pneumonia among the controls, both groups responded in like manner to the acute infections of the respiratory tract observed during the period of drug therapy.

During the time that one gram of sulfadiazine was given daily to the treated group, an outbreak of chicken pox occurred in the cottage. From December 22 to February 9 there were 15 cases (11.5 per cent) and these occurred on the following days:

OCURRENCE OF CASES OF CHICKEN POX IN COTTAGE IOTA

Date of onset	Total number of cases in cottage	Number of cases in study groups		
		Total	Treated group	Control group
December 22	1	0	-	-
23	1	0	-	-
January 1	1	0	-	-
3	1	0	-	-
8	1	1	1	0
9	1	2	1	1
10	2	2	1	1
12	2	0	-	-
19	1	0	-	-
February 9	1	0	-	-
Total	15	5	3	2

Five cases of chicken pox were observed among the 60 children in the study, three among the treated and two among the control children. They all appeared within a period of three days and were mild in both groups, without manifestation of secondary bacterial invasion.

From the foregoing clinical observations it is apparent that there were no significant differences between the treated and control groups in their response both to the common acute respiratory infections and chicken pox prevalent during the period of daily drug therapy. With the exception of a single case of lobar pneumonia in the control group, the infections were mild and uncomplicated by serious secondary bacterial complications. The infrequency of severe bacterial infection during the test period militated

against a satisfactory clinical test of their prevention by the prophylactic daily use of sulfadiazine

The immediate post-therapy period was clinically uneventful. There were no acute febrile respiratory infections in either study group for the first two weeks following discontinuation of daily drug therapy. Later, however, four cases of moderate severity occurred within 10 days, three in the previously treated group and one among the control children. All of these infections were confined to the upper respiratory tract.

About a month after the cessation of daily therapy, an outbreak of scarlet fever occurred, as mentioned above, with an attack-rate for the cottage of 21.5 per cent. During the epidemic period from April 24 to June 2, there were five cases in the treated group and two in the control group. The illnesses were mild in six of the affected children and severe in one, a treated child who developed pneumonia at the onset of the disease. He died three weeks later with an extensive bronchopneumonia. Cultures taken before and after death yielded hemolytic streptococci and *Pneumococcus* type XI. It is interesting that the latter organism was not only recovered from throat cultures from time to time, but by actual test proved to be resistant to sulfadiazine, whereas the former was susceptible to the drug.

### DISCUSSION

The present study differed from the one conducted during the preceding year in the administration of sulfadiazine. In the previous study, the drug was prescribed as soon as symptoms of respiratory disease appeared, since early treatment was the chief expedient. From that experience it was learned that the early adoption of drug therapy may be valuable and beneficial depending upon the susceptibility of the bacteria involved, the dosage prescribed, the duration of treatment, and the tolerance and need of the patient for the drug.<sup>1, 2</sup>

In the present study, sulfadiazine was administered continuously, the purpose being the prevention of bacterial infections of the respiratory tract during the expected period of greatest respiratory morbidity. However, despite the use of the drug for 15 consecutive weeks during the four months of the year when severe infections are usually most prevalent, there were no serious outbreaks for a satisfactory clinical trial of the prophylactic value of the drug. The infections encountered, with the exception of a single case of pneumonia, were relatively mild in both treated and control children, and they appeared to be unaffected by the use of the drug. Under the conditions that prevailed, therefore, no particular advantage was gained by the prolonged application of the drug. In this connection it may be of interest to recall similar studies in rheumatic fever where the continuous use of sulfanilamide appears to reduce the number of exacerbations presumably the result of the drug on the prevention of streptococcal infections.<sup>3-6, 7, 8, 9, 10, 11, 12</sup>

With the progression of the study, several questions, speculated upon by

previous workers as well, presented themselves, and to a measure at least answers have been forthcoming. Foremost among these questions has been the cumulative toxicity of the drug. The evidence obtained in this study reveals that speaking in general terms, it may be said that the toxic reactions stimulated by sulfadiazine need not deter its prolonged use if proper precautions are followed. Secondly, the question of drug sensitization has also arisen, and a partial answer has been obtained. Although none of the children presented any signs interpretable as sensitization, the conclusion should be that the condition may indeed occur, as others have reported, but that its frequency for sulfadiazine, at least, is of low order. In addition, there remain questions, both clinical and academic, pertaining to acquired bacterial resistance. These will have to await presentation and discussion for their appropriate places in subsequent reports on the collateral bacteriological studies described in sections 2, 3, and 4 which follow.

### SUMMARY AND CONCLUSIONS

1 Sulfadiazine was administered to 30 children for a period of 15 weeks, from December 1942 through March 1943, to determine its effect on the bacterial flora of the nasopharynx, and on the frequency, severity, and complications of acute respiratory infections.

2 During the first half of the study, daily dosage was one gram and in the latter half, the dosage was doubled. The concentration of free sulfadiazine in the blood averaged 3.4 mg. per 100 c.c. with the lower dosage, and 7.2 mg. per 100 c.c. with the higher dosage.

3 For purpose of control, 30 additional children comparable with those receiving drug were observed under the same living conditions.

4 Recognizable toxic reactions attributable to sulfadiazine were negligible. Changes in red and white cells and non-protein nitrogen of the blood were all within the range of normal variations. Sulfadiazine crystals and a few microscopic red blood cells were observed commonly in the urines.

5 The respiratory infections encountered were pneumonia, the common cold and chicken pox.

6 There were no significant differences in the frequency and severity of the infections of the respiratory tract observed in treated and control groups.

7 The clinical infections in both groups were few, relatively mild and, with one exception, were not complicated by virulent bacterial invasion so that any prophylactic or therapeutic effect of the drug was not readily demonstrable.

8 Significant changes in the bacterial flora of the nasopharynx were observed and will be described in sections 2, 3, and 4 of the report.

### ACKNOWLEDGMENTS

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# THE EPIDEMIOLOGY OF ACUTE RESPIRATORY INFECTIONS CONDITIONED BY SULFONAMIDES.

## II. GROSS ALTERATIONS IN THE NASO-PHARYNGEAL FLORA ASSOCIATED WITH TREATMENT \*

By L. A. JULIANELLE† and MORRIS SIEGEL, *New York, N. Y.*

THAT sulfonamides exert considerably greater retarding effect on the development of bacteria than viruses, has been too common an experience to require more than passing mention. Consequently, it is not surprising, as previous reports from this laboratory have already indicated,<sup>1, 2, 3</sup> that in the administration of sulfadiazine little influence was observed on the incidence and severity of acute respiratory infections presumably of viral etiology. In organizing the clinical studies, therefore, it became important to measure the effects of drug treatment in terms of changes and fluctuations in the bacterial flora of the upper air passages. In the present communication it is proposed to describe some of the bacteriological observations made in physically normal children under prolonged treatment with sulfadiazine.

### METHODS

As described earlier,<sup>2</sup> two groups, each composed of 30 feebleminded children, were under constant observation from November 1942 to July 1943. One group was given sulfadiazine daily from December 11 to March 25 (15 weeks), the dosage consisting of one gram per diem during the first two months and two grams per diem during the remainder of the time. The second group, while maintained under identical conditions of living, received no drug. The basis on which the children were selected, the method of drug administration during health and infection, and related procedures have already been described in detail<sup>2</sup> so that they need not be repeated in this place.

Simultaneously with the clinical observations, throat cultures were made at first in a variety of ways and culture media. It was found in time, however, that adequate information might be obtained by seeding blood-agar plates with material collected by pharyngeal swab, so that this was the only technique continued. For about the earlier half of the drug treatment, cultures were made in relays covering the 60 individuals within a week, but the schedule was subsequently extended to 10 day intervals. The cultures were incubated in the customary manner and identification of the cultivable organisms was effected by the usual methods.

It was originally planned to quantitate the data, so that the incidence of the different species might be calculated on a numerical basis. As desirable as this may be, no practical or reliable method was found. The procedure finally adopted was to estimate the number of colonies developing on the blood-agar plates and from this estimation to derive an approximate ratio of the different species present.

### EXPERIMENTAL

The pharyngeal cultures taken prior to the period of drug treatment were intended primarily for orientation. They also served to establish the important fact that both groups of children were as similar as could be expected regarding their throat flora. To illustrate that this statement is justified, figure 1 is submitted with a representation of the results observed.

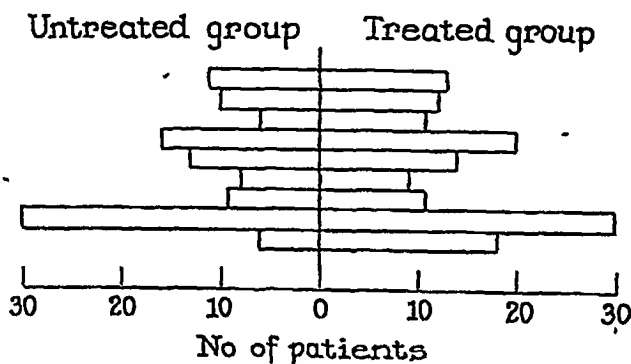


FIG 1 Distribution of different bacteria before drug treatment. Reading downward the organisms represented are *Streptococcus alpha*, *beta*, *gamma*, *Pneumococcus*, *Staphylococcus*, *Sarcina*, *Diphtheroids*, *Neisseriae* and *H. influenzae*.

in the preliminary cultures. Each bar represents the number of individuals carrying the organism designated. A glance suffices to show that while there were minor variations between the two groups, the general character of the graphs is similar for both groups of children.

**Results of the cultures.** During the 15 weeks of drug administration, 9 pharyngeal cultures were seeded from each individual in both treated and untreated groups. The data bearing on the distribution of the different species have been plotted in figure 2. Using the same scheme as adopted in figure 1, the columns themselves represent successive cultures, while the height of the column indicates the number of individuals carrying the organism in question. Analysis of the data reveals that except for *Neisseriae* and hemolytic streptococcus, the different organisms were recovered in somewhat greater numbers in the treated group. Although there are a number of fluctuations apparent for all the species, it can be said that in general the variations are more or less similar for both groups of children. The outstanding exception to this statement is the striking alteration in frequency of the *Neisseriae*, which will be discussed later at greater length.

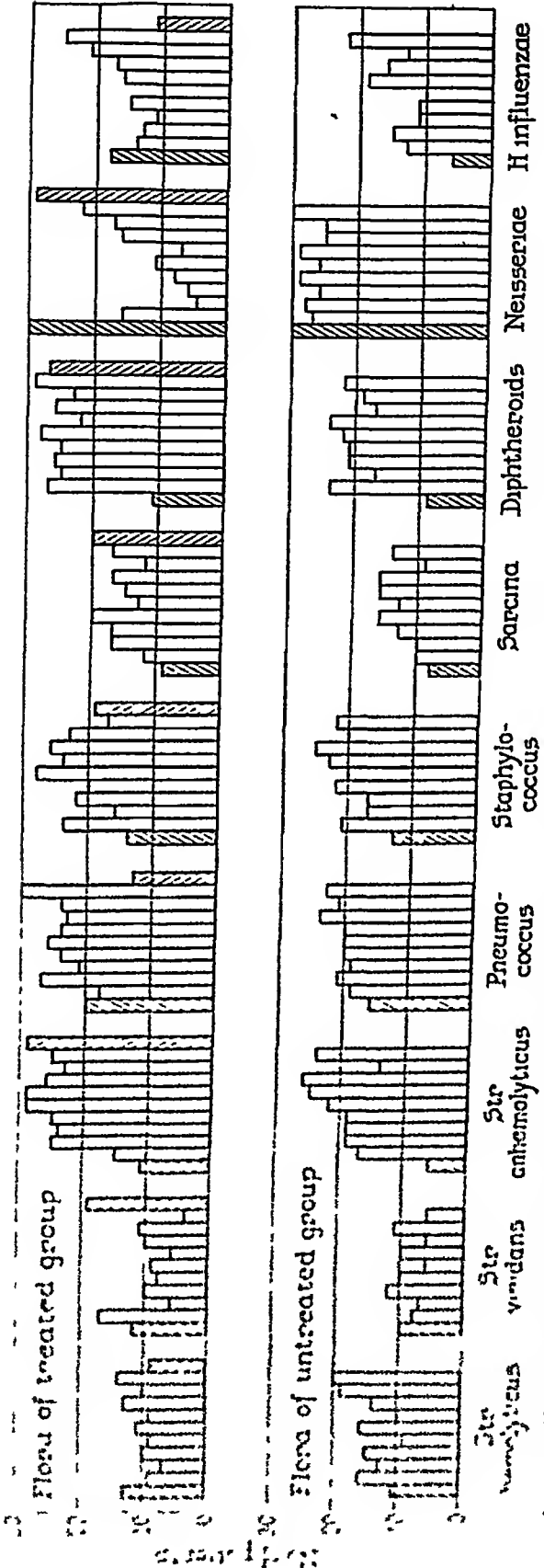


Fig. 1. Frequency of different organisms in treated and untreated children. For each species, the first hatched bar represents the first culture taken a week before therapy, the white bars the results of nine successive cultures during the therapeutic period, and the last hatched bar the results obtained four days after cessation of therapy.

TABLE I  
Frequency of Different Bacterial Species in Pharyngeal Cultures

Organism	Group	Incidence	
		Numerical	Percentile
Neisseriae	Control	250	15.2
	Treated	116	7.1
Diphtheroids	Control	207	12.5
	Treated	249	15.2
Pneumococcus	Control	200	12.2
	Treated	229	14.0
Staphylococcus	Control	200	12.2
	Treated	219	13.3
Streptococcus gamma	Control	197	12.0
	Treated	244	14.9
<i>H. influenzae</i>	Control	155	9.4
	Treated	163	10.0
Streptococcus beta	Control	153	9.3
	Treated	103	6.3
Sarcina	Control	129	7.8
	Treated	149	9.1
Streptococcus alpha	Control	83	5.0
	Treated	91	5.5
Miscellaneous	Control	72	4.4
	Treated	75	4.6
Total	Control	1646	100
	Treated	1638	100

To help simplify presentation of the data, a summary protocol (table 1) is appended to illustrate the relative frequency of the species during administration of sulfadiazine. If, first of all, the occurrence of any species is considered as a single unit, irrespective of whether it was the same or different organism, then it may be said that there was a total of 1646 isolations in the control group as compared with 1638 in the treated group. Among the controls, Neisseriae with 250 isolations were the most frequent of all the organisms encountered, with the order of frequency proceeding with diphtheroids, pneumococcus, staphylococcus, indifferent streptococci, Streptococcus gamma, *H. influenzae*, Streptococcus hemolyticus, Sarcina, Streptococcus viridans, and finally, a scattering of miscellaneous forms. In the treated group the diphtheroids with 249 isolations predominate with indifferent streptococci, pneumococcus, staphylococcus, *H. influenzae*, Sarcina, Neisseriae, Streptococcus beta and alpha, and, last of all, the miscellaneous bacteria in the order named. The discrepancies immediately apparent between the treated and untreated children are found in both the



*Neisseriae* and hemolytic streptococci. In the untreated group the *Neisseriae* are more than twice as frequent, and the hemolytic streptococci were half again as frequent as in the treated group. The implication is obvious that sulfadiazine induced a bacteriostatic effect on the former organisms, and although not so definite, there is a suggestion of similar though less extensive activity on the latter.

Other organisms than those classified above were identified from time to time in the cultures. Because their number was not great and their frequency not regular, no need was felt for discussing them. That the records may be kept complete, it is desirable to catalogue the species encountered. Most numerous of the rarer forms were the gram-positive cocci of the tetrads group. Occasionally, the colon bacillus was isolated, as were monilia, streptothrix, unidentified fungi, and members of the subtilis group which were in all probability merely contaminants. Because of their rare appearance, no statement can be made as to whether sulfadiazine had any effect on their presence or incidence. It is interesting that Friedlander's bacillus was never isolated, as was also true of meningococcus.

It seems desirable at this point to comment briefly on the individual species isolated during the course of observations. Of the streptococci, the indifferent or gamma forms were most commonly encountered in both the drug-treated and untreated children. They ran consistently higher in the individuals receiving sulfadiazine, and the drug manifested no measurable reduction on their incidence. Next in frequency came the hemolytic or beta variety. In this case, the cocci were more numerous in the untreated group. The viridans or alpha *Streptococcus* appeared in the least number of patients, only rarely (two occasions) occurring in more than half of either group. Their incidence was lower in the untreated individuals and the drug was apparently unable to reduce their numbers significantly. In all three organisms there were fluctuations with successive cultures in the proportion of drug-treated children carrying the cocci, but these were irregular and in general simulated the changes observed in the untreated group.

Pneumococci were found with a high degree of regularity throughout the survey in both treated and untreated children alike. It will be observed in figure 2 that these organisms ran moderately higher in the drug-treated group, and in both cases they proved to be present in a high proportion of the total flora. In spite of the lengthy course of sulfadiazine, there was no visible gross effect on the number of pneumococci cultivable from the treated individuals. This came in the nature of a surprise since it had been anticipated that a reduction would sooner or later make itself manifest. A study of the types involved, however, clarified completely what appeared to be a paradox. Owing to the number of experiments undertaken and the space required to describe and explain the observations, it seems wiser to reserve all discussion of this organism for a later communication.

Staphylococci were also present in a large number of the cultures. Their frequency ran slightly higher in the treated children, but their proportion

from culture to culture paralleled that observed in the untreated group. Consequently, it is felt that this species was not affected by the prolonged exposure to sulfadiazine resulting from the daily administration. It may be of interest to compare the ratio of *aureus* and *albus* strains in both groups of children. Thus, the proportion of *aureus* to *albus* strains in the untreated group was approximately 1:3.4 and 1:3.2 in the treated group. The predominance of *albus* strains was to be anticipated, perhaps, since speaking in general terms, the large majority of staphylococci harbored in the normal throat are saprophytic which in turn are usually, not always, of the *albus* variety. Another point of interest was the proximity of the ratios in both groups of children, which indicates in another way, perhaps, the absence of any action by the drug.

Sarcinae comprised the last of the gram-positive cocci to be described. Their incidence was low, although a trifle greater in the treated children. Apparently they were not influenced by sulfadiazine.

Of the gram-positive rods, the *Corynebacteria* only require comment. Diphtheroids were present commonly in the throat cultures and they persisted throughout the period of observation. Several weeks after the study was begun, a diphtheria carrier was detected among the treated children. The organism spread rapidly, creating conditions for a more specialized study which will be reported appropriately in a subsequent communication. It may be said that in both instances, however, their frequency was not limited by continuous administration of sulfadiazine.

The gram-negative organisms were represented almost entirely by *H. influenzae* and the different *Neisseriae*. Members of the *Hemophilus* group consisted essentially of *H. influenzae*. Occasionally, the hemolytic variety was found, but its presence was neither constant nor numerous. In any case, these organisms did not play a prominent part in the bacterial flora and, as far as could be determined, no effect was induced upon them by the sulfadiazine.

In commenting on the *Neisseriae*, it must be said that no serious classification of the different species of gram-negative cocci was attempted, chiefly because the action of the drug was generalized and included each variety observed. The data bearing on these organisms are submitted graphically in figure 3 and they show both the reduced distribution in the treated individuals and, more importantly, the changing frequency of gram-negative cocci occurring in the cultures. The height of each column represents the number of children carrying the organisms. In order to illustrate the number of colonies isolated in each culture, each column has been divided to represent growth as + + + +, + + +, + +, + and  $\pm$ . + + + + signifies *Neisseriae* were the predominate organisms of a culture, + + + second in predominance, + + third, + fourth and  $\pm$  fifth or beyond.

Examination of the data indicates that although the frequency of cultures containing gram-negative cocci and the relative number of colonies per culture ran remarkably alike in both groups before the drug was started, there

was a rapid and marked divergence immediately afterwards. In the control children, the distribution of *Neisseriae* maintained a more or less consistent status in the nasopharyngeal flora, so that they retained their relative prevalence with insignificant variations during the entire period of drug therapy. Among the treated children the predominance of gram-negative cocci fell rapidly, so that within three to seven days after drug therapy began they were not isolated in almost half of the cultures. During the first month

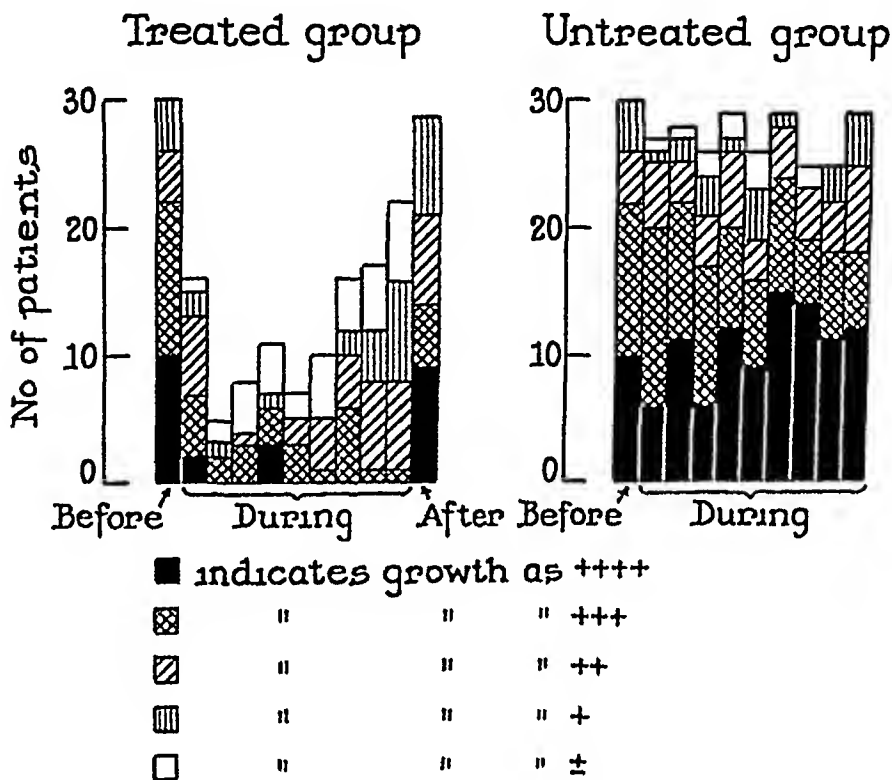


FIG. 3. Distribution of *Neisseriae* by individuals and their numerical frequency in culture.

of drug therapy, either no colonies or relatively few colonies of gram-negative cocci could be isolated. After that, despite doubling of sulfadiazine dosage, the frequency of positive cultures increased progressively, although the number of colonies per culture still remained low in many instances. Shortly after withdrawal of the drug, the *Neisseriae* returned to their original frequency. The changes described were so marked and characteristic that most of the treated and control cultures could be differentiated from each other by the relative prevalence of *Neisseriae* on the blood agar plates.

The striking differences observed between the two groups are summarized in table 2. During the period of drug therapy, the *Neisseriae* were the prevailing organism in only 2 per cent of the cultures taken in the treated group as compared with 35 per cent of those taken in the control group, and second most numerous in 9 per cent of the treated in contrast to 30 per cent of the controls. Moreover, the gram-negative cocci were completely

TABLE II  
Numerical Frequency of Neisseriae in Nasopharyngeal Cultures  
of Untreated and Treated Children

Degree of Growth	Treated group		Untreated group	
	Number	Per cent	Number	Per cent
++++	5	1.9	106	35.3
+++	25	9.3	90	30.0
++	32	11.8	44	14.7
+	18	6.7	23	7.7
±	36	13.3	11	3.7
0	154	57.0	26	8.7
Total	270	100.0	300	100.1

The plus signs may be interpreted as +++++, most numerous of all the different organisms isolated, +++ as second most numerous, etc., while 0 indicates no Neisseriae were isolated.

absent in almost 60 per cent of cultures from treated children as compared with less than 10 per cent for the controls.

Another point of interest concerns the permanency of the disappearance of Neisseriae during continued administration of sulfadiazine. The data analyzed for this purpose are tabulated in table 3. The disappearance has been classified as prolonged, intermittent and transient. By prolonged is

TABLE III  
Changes in Neisseriae with Administration of Sulfadiazine

Groups	Total number of children	Disappearance of Neisseriae			No change
		Prolonged	Intermittent	Transient	
Untreated	30	0	4	11	15
Treated	30	15(6*)	8	1	0

\* The continuity in these six individuals was interrupted by a single or two inconsecutive appearances of Neisseriae.

meant failure to recover gram-negative cocci on culture during a period of 7 to 10 weeks, intermittent implies alternating success and failure in the cultivation of Neisseriae, transient indicates failure in a single culture or on two scattered occasions. The data reveal that in 15 or half of the treated individuals the disappearance of Neisseriae was prolonged, to this number must be added six more children whose long run of "negative" cultures was interrupted once or twice by the presence of a few colonies. Also in this group there were eight examples of intermittent and only one of transient disappearance, with not a single child unaffected by the drug. In the untreated group there were no prolonged disappearances of Neisseriae, 4 intermittent, 11 transient and 15 in whom no changes were observed from culture to culture.

The abnormal changes observed among the gram-negative cocci occurring in the pharynx were subsequently related to acquired resistance to sulfadiazine. A few weeks before terminating drug treatment, a number of strains were isolated for the purpose of determining their resistance to varying concentrations of drug. For this purpose, 10 strains were selected at random from the control children and seven from the children who had received the drug. For the sake of brevity, the growth of several strains, considered as typical, have been tabulated (table 4) to illustrate the types of reaction observed. Thus, measuring first the growth in drug-free broth as the maximum for that particular strain, the development in the same broth containing increasing concentrations of sulfadiazine from 1 mg. to 25

TABLE IV  
Illustration of Reaction of Neisseriae to Sulfadiazine

Strain number and source	Degree of growth in							
	Drug-free medium	Medium containing sulfadiazine						
		*1	2	3	5	9	12	25
N24—Untreated	++++	—	—	—	—	—	—	—
N26—Untreated	++++	++	—	—	—	—	—	—
P45—Untreated	++++	++++	++++	+++	+++	++	+	—
N29—Untreated	++++	++++	++++	++++	+++	+++	+++	+++
N37—Untreated	++++	++++	++++	++++	+++	+++	+++	+++
R27—Treated	++++	++++	++++	++++	+++	+++	+++	+++
R57—Treated	++++	++++	++++	++++	+++	+++	+++	+++

The degree of growth is indicated by different graduations ranging from maximum (++++), to no growth (—).

\* These figures indicate concentration of drug as so many milligrams per 100 c.c. of medium.

mg. per 100 c.c. of medium was noted and graded correspondingly. The assembled data illustrate that susceptible strains (e.g., N24 and N26) were unable to withstand as little as 2 mg. of sulfadiazine per 100 c.c. of broth. A single strain was considered as intermediate or partially resistant to the drug (N45). This strain isolated from one of the untreated children grew poorly to be sure, but in a concentration of 12 mg. per 100 c.c. Resistant strains both from treated and untreated children withstood without appreciable difficulty concentrations of 25 mg. per 100 c.c., the highest concentration to be tested.

The occurrence of resistant strains among the untreated group as well as among the treated requires explanatory comment. During the period of drug treatment the contact between the two groups of children was very intimate, so that strains undoubtedly passed freely between both groups. Thus, in an untreated individual (No. 16) the culture isolated during the time sulfadiazine was administered was so susceptible that it failed to grow in a concentration of sulfadiazine of 2 mg. per 100 c.c. of broth. About a month later, after cessation of the drug in the treated group, another culture isolated from the same child was able to grow in a concentration of

25 mg per 100 c c In this case, the fastness must be interpreted as a likely transfer of a resistant strain to him from one of the treated children

If the data pertaining to drug-fastness are now summarized (table 5) it is seen that all seven strains isolated from the treated children proved to be resistant to sulfadiazine Of the 10 strains originating from the untreated children, five were susceptible, one was partially resistant, and four

TABLE V  
Summary of Experiments on Resistance of Neisseriae to Sulfadiazine

Strains isolated from	Number of strains and reaction to drug			Total strains
	Susceptible	Intermediate	Resistant	
Untreated group	5	1	$\frac{1}{2}$	10
Treated group	0	0	7	7

equalled the resistance observed in the case of the strains from the opposite group The important point is that among the subjects receiving sulfadiazine, none of the strains tested was found susceptible The conclusion seems clear, therefore, that with administration of sulfadiazine, the disappearance of the Neisseriae was due to a susceptibility of the organism to the drug, the reappearance, on the other hand, even under prolonged and increased treatment, was associated with an acquired tolerance or resistance to the drug

### DISCUSSION

The most striking effect observed of the continuous administration of sulfadiazine in physically normal children was brought into evidence by a rapid disappearance of gram-negative cocci from the nasopharynx The sequence of events observed was first the actual disappearance of Neisseriae from the majority of treated individuals, then their gradual return in spite of doubly increasing the dosage of sulfadiazine and finally, the demonstration in vitro of the drug susceptibility of the organisms from the untreated children as contrasted with the drug resistance of those from the treated children

Less striking and perhaps only suggestive was the evidence gathered on the inhibition of hemolytic streptococci Perhaps because these organisms were never numerous, it may be that the action of sulfadiazine was not so readily detected Yet the more frequent occurrence of these cocci as well as their greater numbers per plate in the untreated children suggests a possible but not extensive effect of the drug on hemolytic streptococci This possibility is now under study in healthy carriers

It is further interesting that in spite of numerous fluctuations in the frequency of the different organisms, the total isolations from both groups of children ran remarkably close This may have been due entirely to chance

Yet, one wonders, nevertheless, whether the fluctuations may not represent a state of balance attained by a numerical compensation of one species over another, in which case, there might be a factor of some kind operative under certain undefined conditions to limit the population of different bacterial species multiplying in the same environment. Such a factor might then explain not only the presence or absence of specific organisms, but even the ascendancy of one species on the suppression of another.

From either the medical or public health aspect, the results on the gram-negative cocci reaffirm a repeated clinical observation that where sulfonamides are effective, their action is prompt and usually conclusive. It is not necessary, therefore, to continue administration, provided the dosage is adequate, if during the first few days the effect is questionable or nil. Of epidemiological interest is the disturbing fact that with prolonged use of the drug, the previously susceptible strains not only become resistant, but they may even spread through an exposed population.

#### SUMMARY AND CONCLUSIONS

- 1 Prolonged treatment of physically normal children with sulfadiazine causes changes in the bacterial flora of the throat, as demonstrable on blood-agar plates.

- 2 The most striking change is a rapid disappearance of the gram-negative cocci.

- 3 This action is transitory, however, since the cocci return in their original frequency in spite of continued treatment.

- 4 Associated with the reappearance of the gram-negative cocci, it is possible to show an exalted tolerance for the drug on the part of the bacteria.

- 5 Although the numerical incidence of pneumococcus remains more or less constant during treatment, there is evidence, not now described, of great changes in immunological types.

- 6 The effect on hemolytic streptococci is not conclusive, but the data suggest a partial inhibitory action by sulfadiazine.

- 7 Other organisms as staphylococci, *Streptococcus* alpha and gamma, diphtheroids, *Sarcina*, *tetragenus* and *H. influenzae* are not noticeably affected under the conditions outlined.

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# THE EPIDEMIOLOGY OF ACUTE RESPIRATORY INFECTIONS CONDITIONED BY SULFONAMIDES.

## III. EFFECTS OF TREATMENT ON THE ORGANISM AND CARRIER OF DIPHTHERIA \*

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### INTRODUCTION

DURING the course of observations on the changes in the bacterial flora of the upper respiratory passages associated with prolonged administration of sulfadiazine, the organism of diphtheria was unexpectedly isolated from the throats of two children receiving the drug. As will be recalled from the preceding reports in this investigation,<sup>1, 2</sup> a study was in progress on 60 children, half untreated in any way and the other half treated for 105 consecutive days with sulfadiazine. The purpose was to determine what effect this treatment might have on acute respiratory infection and in what way it might influence the organisms cultivable from the nasopharynx. With the appearance of *C. diphtheriae*, careful clinical examination of the carriers was made but no abnormal signs or symptoms were uncovered. Skin tests with diphtheria toxin (i.e., Schick test) were performed in the usual manner and they indicated that all the children under observation were so-called "immune." It was decided, therefore, to allow dissemination of the organism to proceed without interference in order to ascertain both its mode of spread and its behavior under sulfonamide therapy.

Upon questioning of the medical officers in charge at the institution, it was learned that in the past an occasional case of nasal diphtheria, which was not severe in character, had been encountered in the cottage housing the children under study. Presumably, then, the original source of the organism was in some of the children who, while living in the same cottage, were not included in the present survey. If this assumption is correct, an explanation is readily furnished for the absence of the organism in the earlier cultures of the children studied.

### EXPERIMENTAL

*Dissemination of C. diphtheriae during treatment.* The administration of sulfadiazine was begun on December 11 (1942), and for the 240 cultures studied in relays up to January 4, *C. diphtheriae* was never observed. On

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† Died, August 12, 1944.





strains from treated children, 13 strains from untreated children, and two from the attendants. The reaction of these strains in media containing phenol red as indicator, serum and various carbohydrates was first determined and a summary of these reactions is to be found in table 1. All 46 strains behaved in similar fashion, causing acid and coagulation in dextrose, and acid in variable degrees of intensity in dextrin. In lactose, sucrose, mannite, glycogen and starch, the growth was accompanied by no visible change in reaction.

TABLE I  
Reaction of 46 Strains of *C. diphtheriae* in Carbohydrates

Strains		Reaction in						
Number	Source	Dextrose	Dextrin	Lactose	Sucrose	Mannite	Glycogen	Starch
18	Untreated group	All AC	All A	NR	NR	NR	NR	NR
26	Treated group	All AC	All A	NR	NR	NR	NR	NR
2	Attendants	All AC	All A	NR	NR	NR	NR	NR

AC—Indicates acid and coagulation    A—Indicates acid only    NR—Indicates no reaction

In classifying further the 46 strains studied, a note was made of their microscopic appearance, effect on rabbit blood (in agar plates), character of growth on tellurite agar, and toxigenicity as measured in the guinea pig. Microscopically, all the strains suggested the *mitis* form. On rabbit blood agar plates, all but two strains were hemolytic, and these formed an area of methemoglobin around each colony. One of the two strains was isolated from an untreated and the other from a treated child. On tellurite agar, the hemolytic strains were typical of the *mitis* variety, while the two producing methemoglobin suggested the *intermedius*. The colonial appearance of the latter differed in some respects from the typical form, so that there is a hesitancy in labeling the two strains definitely as such.

*Virulence of the strains.* Tests for toxigenicity were carried out on the basis of screening tests. Pools were made of three or four cultures by emulsifying the growth from Loeffler slants (18 hours' incubation) with 10 c c of broth. The suspensions were then pooled and from the pool 10 c c was taken and injected subcutaneously into guinea pigs weighing approximately 250 grams. Although it is realized that the dosage adopted was large, it was deliberately selected because from the clinical histories a low toxicity was suggested. In case the animals survived, all the strains composing the pool were regarded as non-toxicogenic. In case of death, an autopsy was performed. If organisms were cultivable and stainable from the original site, if a gelatinous edema surrounded the area of inoculation, and if the adrenals appeared to be enlarged and hemorrhagic, the pool was broken down into its component strains and retested as individual cultures. The results of the tests for toxigenicity are summarized in table 2. Thus of the 18 cultures derived from the untreated children six were characteris-

TABLE II  
Classification of 46 Strains of *C. diphtheriae*

Strains		Microscopic appearance	Effect on rabbit blood	Growth on tellurite	Toxicity per guinea pig
Number	Source				
18	Untreated group	All <i>mitis</i>	1 methemoglobin 17 hemolytic	1 <i>intermedius</i> ? 17 <i>mitis</i>	6 toxic 12 non-toxic
26	Treated group	All <i>mitis</i>	1 methemoglobin 45 hemolytic	1 <i>intermedius</i> ? 25 <i>mitis</i>	1 toxic 25 non-toxic
2	Attendants	All <i>mitis</i>	2 hemolytic	2 <i>mitis</i>	2 non-toxic

Effect on rabbit blood was determined by growth on blood agar

The two strains listed as questionable *intermedius* were suggestive of this variety but the characteristics were not completely conclusive

The toxic strains in the untreated group represent six isolations from three individuals or, actually, only three different strains

tically toxigenic and 12 nontoxigenic. However, since the six strains were isolated from three individuals at different times it can be said that actually only three different strains produced toxin. Of the 26 strains isolated from the treated group, only one was toxigenic. It may be of interest to add that after survival of the guinea pigs receiving pooled cultures was established, all the animals were subsequently tested for immunity to diphtheria toxin. Within a period varying from 10 days to three weeks after the injection of cultures, the guinea pigs were inoculated intraperitoneally with 10 M.L.D. of toxin. In each case, death followed within 24 hours with typical signs of diphtheria intoxication. This, then, is another way of demonstrating the nontoxigenicity of the strains in question.

TABLE III  
Recapitulation of Characteristics of *C. diphtheriae*

Strain	Group	Reaction on			Toxicity
		Rabbit blood	Tellurite	Serum	
No. 23	Untreated	Methemoglobin	<i>intermedius</i> ?	Typical	+
No. 35	Treated	Methemoglobin	<i>intermedius</i> ?	Typical	+
No. 24	Untreated	Hemolytic	<i>mitis</i>	Typical	-
No. 3	Untreated	Hemolytic	<i>mitis</i>	Typical	-
All other 12 strains	Both	Hemolytic	<i>mitis</i>	Typical	0

reactions in sugar The remaining strains studied were all avirulent, hemolytic, and appeared to be typical of the *mitis* variety, both on tellurite agar and in sugars

On first analysis, it appears that the 46 strains partition themselves into three varieties methemoglobin-producers and toxigenic, hemolytic and toxigenic, hemolytic and nontoxigenic On second consideration, however, the thought cannot be dismissed that the dissimilarities enumerated are perhaps minor and that they may represent not essential differences, but evidences of degradation or variation from an originally common or identical strain

*Reaction of C. diphtheriae to sulfadiazine* In continuing with the investigation, it was found of interest as a co-related problem to determine the effect of sulfadiazine on the organisms isolated For this purpose, 16

TABLE IV  
Growth of *C. diphtheriae* in Broth Containing Sulfadiazine

Strains		Control	mg of sulfadiazine per 100 c.c. of broth						
Number	Source		5	8	12	25	50	75	100
B24	Untreated group	++++	++++	++++	++++	++++	++++	++++	++++
N24	Untreated group	++++	++++	++++	++++	++++	++++	++++	++++
3	Untreated group	++++	++++	++++	++++	++++	++++	++++	++++
23	Untreated group	++++	++++	++++	++++	++++	++++	++++	++++
32	Untreated group	++++	++++	++++	++++	++++	++++	++++	++++
N32	Untreated group	++++	++++	++++	++++	++++	++++	++++	++++
7	Untreated group	++++	++++	++++	++++	++++	++++	++++	++++
15	Untreated group	++++	++++	++++	++++	++++	++++	++++	++++
C38	Treated group	++++	++++	++++	++++	++++	++	++	++
322	Treated group	++++	++++	++++	++++	++++	++	++	++
R22	Treated group	++++	++++	++++	++++	++++	++	++	++
18	Treated group	++++	++++	++++	++++	++++	++	++	++
18	Treated group	++++	++++	++++	++++	++++	++	++	++
D58	Treated group	++++	++++	++++	++++	++++	++	++	++
P58	Treated group	++++	++++	++++	++++	++++	++	++	++
235	Treated group	++++	++++	++++	++++	++++	++	++	++
Park No 8		++++	++++	+++	+++	++	++	+	+

strains were selected at random and their reaction to the drug was first studied in vitro For orientation, similar tests were performed with the Park No 8 strain The tests were performed by adding to beef-infusion broth, concentrations of sulfadiazine varying from 50 mg per 100 c.c. to 100 mg per 100 c.c. Inoculations were made with 0.1 c.c. of 18-20 hour broth culture Similarly, broth not containing sulfadiazine was inoculated with each strain The growth obtained in this case was regarded as + + + +, and this was used as a standard for comparison for growth of the same organism in medium containing sulfadiazine The experiment was repeated in parts, two to four times, with variable results, due presumably to both the growth-promoting factors for *C. diphtheriae* and the sulfonamide-blocking substances contained in the medium The data pertaining to the experiment will be found assembled in table 4 It will be seen that although minor variations in the degree of tolerance are evident, the statement can justifiably be made that the strains tested were resistant to sulfadiazine One

other point worthy of comment is that in several cases, strains isolated both early and late from the same individuals were studied for possible increased tolerance to the drug without, however, detecting any appreciable differences.

*Effect of sulfadiazine on toxin* Since no bacteriostatic action of importance was demonstrable, experiments were next projected to establish any influence of the drug on the toxic properties of the organism. This was done by first determining the effect on preformed toxin and secondly, by observing the effect on the elaboration of toxin by cultures themselves resistant to the drug. In the first experiment, diphtheria toxin\* in quantities of 10, 20 and 50 M.L.D. were each mixed with sulfadiazine to give concentrations of the drug of 5, 8 and 12 mg per 100 c.c. The mixtures were incubated at 37° C. for four hours, when they were inoculated subcutaneously in guinea pigs weighing about 250 grams. This made a total of nine animals, all of which died within 24 hours. Autopsy revealed typical signs of intoxication. Although the experiment might have been extended to include greater concentrations of sulfadiazine and longer periods of incubation, the preliminary results discouraged further trials. Under the conditions of the experiment, then, no effect was observed by the action of sulfadiazine on diphtheria toxin.

In the second experiment, the effect of sulfadiazine on the elaboration of toxin was studied. Three strains isolated from individuals under observation were used, and for control purposes, the Park No. 8. Different concentrations of drug varying from 5 mg. to 50 mg. per 100 c.c. of medium were added to broth which was then inoculated individually with the four strains. After nine days' incubation, filtrates obtained from the cultures were inoculated into guinea pigs to detect the presence of toxin. It is necessary to say only that compared with the results in media without drug, sulfadiazine appeared to have no inhibitory influence on the elaboration of toxin.

*Effect of sulfadiazine on experimental infection* In parallel with the two preceding experiments, a study was made of the therapeutic value of sulfadiazine in active infection by *C. diphtheriae*. Cultures grown on Loeffler's medium for about 18 hours were harvested in 10 c.c. of broth. This was then inoculated subcutaneously into two guinea pigs followed immediately by intraperitoneal injection of 0.05 gram of sulfadiazine. Administration of drug was then continued at this dosage twice a day until the experiment was terminated. The strains tested were the Park No. 8 and No. 23 isolated in this study. For control study, a single animal was inoculated with virulent culture but was denied sulfadiazine. Other controls consisted of guinea pigs similarly treated with an avirulent culture and drug, and two other animals injected with drug alone over a period of five days. The result of the experiment disclosed a failure on the part of sulfadiazine to protect guinea pigs treated with under the conditions stated. The results of the experiment are summarized in Table 1. It is noted that

jected with avirulent culture and drug, or drug alone suffered no ill consequences. Death in each case was that typical of diphtheritic infection. The evidence indicates, as the *in vitro* studies had already suggested, that sulfadiazine is not effective in diphtheritic infection. This conclusion is considered to be a confirmation of similar studies reported on the use of sulfonamide in experimental infection of guinea pigs.<sup>4</sup>

### DISCUSSION

The studies recorded in this report on *C. diphtheriae* were not intended as a classification of the species. Rather was it the purpose to establish the variety of the strains isolated during the present survey and then to continue with the object at hand, of ascertaining their response to sulfadiazine. Consequently, having identified the large majority (44 of 46 strains) as the *mitis* variety, with the two remaining strains as questionable *intermedius*, or better perhaps as indeterminate, it was still considered possible that all the cultures may have originated from a single strain. That only four of 29 strains tested were toxigenic was not surprising, because the experience over the past several years in the cottage housing the children has been that clinical infections were rare and limited to a relatively mild, nasal affection. Even in these cases, the strains must be considered weakly toxigenic because of the large dosages employed for the injections. Evidence corroborating this experience is perhaps furnished by the fact that despite the dissemination of the organism in 30 of the 60 children under observation and in two attendants, there was not a single instance of clinical infection, even in the four children carrying toxigenic strains.

The observation that the organism was recovered in children under sulfadiazine treatment suggested immediately its tolerance to the drug. In the one case of a toxigenic strain in a child of the treated group, the inference was also obvious that the drug did not inhibit formation of toxin. The tests performed *in vitro* on bacteriostasis, elaboration of toxin, and inactivation of preformed toxin succeeded in establishing as facts the impressions gained by clinical observation, since in all three no effect was exerted by sulfadiazine in various concentrations. Similarly, the treatment of experimental infection in guinea pigs by large dosage of drug failed to affect the usual course of fatal intoxication. It is interesting to point out that in a preceding report<sup>2</sup> it was likewise shown that prolonged administration of the drug in children had no effect on the frequency or numbers of the closely allied organisms, the diphtheroids. The drug-fastness of the different strains of *C. diphtheriae* isolated from treated and untreated children, or at early and late stages of treatment was approximately the same, indicating an original high resistance which was not demonstrably increased by continuous administration of sulfadiazine.

## SUMMARY AND CONCLUSIONS

1 Continuous administration of sulfadiazine did not prevent either the dissemination of *C. diphtheriae* among exposed children or its repeated recovery from throat cultures

2 Sixty-eight strains of *C. diphtheriae* were isolated from 30 children, 38 from 17 children under treatment with sulfadiazine, and 30 from 13 children not so treated, and two other strains from attendants

3 A classification was made of 46 strains, 18 from 14 untreated children, 26 from 13 treated children, and two from attendants

4 With the exception of two questionable *intermedius* or indeterminate strains, the organisms were of the *mitis* variety

5 It is possible that the indeterminate strains represent variations from a common parent strain

6 Bacteriostatic tests performed with sulfadiazine revealed that 16 tested strains isolated from the children under study, as well as the Park No. 8 strain were resistant to high concentrations of the drug

7 Sulfadiazine under the conditions outlined above did not inactivate preformed toxin, nor prevent the elaboration of toxin

8 In experimental infection, administration of sulfadiazine as described was ineffectual as a method of treatment

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# THE EPIDEMIOLOGY OF ACUTE RESPIRATORY INFECTIONS CONDITIONED BY SULFONAMIDES.

## IV. TRENDS IN PNEUMOCOCCAL TYPES INITIATED BY DRUG TREATMENT \*

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IN an earlier communication,<sup>1</sup> the occasion was taken to comment on the observation that judged by superficial examination, the continual use of sulfadiazine exerted little effect on the frequency of pneumococcus in the throat cultures of physically normal children. It was intimated, however, that underneath the surface this organism was actually participating in a profound process reminiscent of natural selection. It is proposed to submit in the present report a detailed account of the alterations observed and to describe the correlated experiments undertaken to explain their occurrence. The general method employed in handling the children, half under sulfadiazine treatment and the other half untreated, the manner of taking cultures and carrying them through, etc., have all been described elsewhere.<sup>2</sup>

### EXPERIMENTAL

Cultures were taken preliminarily to establish the bacterial flora of the nasopharynx under so-called normal conditions, so that in this way a base line could be drawn of the types present before treatment was begun. The types of pneumococci isolated were ultimately recognized by the *quellung* reaction but in determining types, the method adopted as simplest and most accurate was to immerse a swab carrying the inoculum from the patient's throat directly into "pneumococcus broth" containing horse blood. The medium was then incubated together with the swab, overnight. On the following morning (about 16 hours) the mixed broth culture was used for direct microscopical typing‡. This method was found far superior to typing either from blood agar plates or from inoculated white mice because of three advantages: (1) virulent as well as avirulent organisms were recovered, (2) a much higher proportion of multiple types was detected than by the other two methods, and (3) because of the directness of the technic, considerable time and manipulation were saved. As will be brought out later, a certain number of strains could not be classified into types, in which case the diagnosis of pneumococcus was assured by mouse virulence, bile solubility, and

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‡ The antisera used for typing was graciously supplied by the Lederle Laboratories and the Bureau of Laboratories of the New York City Health Department.



in some instances by demonstration of capsules. Not all cultures were mouse virulent, but it was felt that even in the absence of this attribute reliance could be placed upon the other two properties.

The cultures taken preliminarily before beginning administration of sulfadiazine disclosed types VI, XI, XII, XVIII, XIX and XXI to be present among both groups of children, although it is felt that with the paucity of data no accurate statement can be made about predominance of types. As already described,<sup>2</sup> pneumococcus was found in great frequency throughout the period of treatment, running somewhat higher for some reason or other among the treated children. Examination of cultures on blood agar plates indicated that sulfadiazine was having little gross effect on its frequency. With the determination of types, however, it soon became obvious that the individual types were undergoing striking changes.

TABLE I  
Distribution of Pneumococcal Types during Period of Treatment

Type of pneumococcus	Untreated group		Treated group	
	Number	Per cent	Number	Per cent
I	11	7.7	1	0.5
III	3	2.1	0	—
VI	29	20.4	7	3.8
IX	6	4.2	3	1.6
XI	14	10.0	115	61.1
XII	1	0.7	2	1.1
XV	0	—	2	1.1
XVI	0	—	3	1.6
XVII	1	0.7	0	—
XVIII*	17	12.0	17	25.5
XIX	1	0.7	1	0.5
XXI	3	2.1	1	0.5
XXII	1	0.7	0	—
XXIII	19	13.4	0	—
XXIV	0	—	3	1.6
XXV	6	4.2	1	0.5
Totals	142	99.9	184	99.7

\* Serologically related to type 18A or type 44.

*Distribution of types during treatment.*—During the period of treatment, a total of 332 strains of typable pneumococci were recovered, of which 142 came from the untreated children and 184 from the treated children. In addition, there were 12 untyped strains from the former and 15 from the latter. In the untreated group, the predominant types in their order of frequency were XI, VI, XXIII, XVIII, I, IX and XXV, with an untypable

Among the children given sulfadiazine, trends in types began to manifest themselves quite early, types XI and XVIII became more and more frequent almost to the exclusion of all other types, accounting between themselves, in fact, for roughly 87 per cent of the total types demonstrated. The order of frequency in this group was in marked contrast to that observed in the control group. Thus, type XI comprised 61 per cent of the strains isolated, type XVIII, 26 per cent, type VI, 4 per cent, types I and XXV, less than 1 per cent each, and scattered types made up the remaining 8 per cent (see table 1). These consisted of types IX, XII, XV, XVI, XIX, XXI, XXIV and XXV. Interestingly enough, some of the types encountered in the untreated group did not occur in the treated children, as, for example, type XXIII. Another comparison of possible noteworthiness is that although the bulk of the individuals studied yielded types with uniformity upon culturing, a few, on the contrary, showed pneumococci only rarely. Thus, in the untreated group, one child (No 3 below) only once presented a typable strain (VI), another (No 24) only twice, and a third (No 20) only three times. Among the treated children, one yielded a type only twice and two others (No 42 and No 50) three times.

TABLE II  
Occurrence of Multiple Types during Period of Treatment

Combination of	Untreated group			Treated group		
	Total	Types XI and XVIII		Total	Types XI and XVIII	
		Number	Per cent		Number	Per cent
Two types	23	4	17.4	34	28	82.4
Three types	6	2	33.3	5	4	80.0
Totals	29	6	20.7	39	32	82.0

An additional observation of interest regarding the effect of sulfadiazine on pneumococcal types was furnished by an analysis of the cultures containing mixed or multiple types. The data appended in table 2 indicate that in the untreated children 23 or 16 per cent of the recovered types occurred as mixtures of two types and six or 4 per cent were mixtures of three types. These figures compare equably with those from the treated children 34 or 18 per cent with two types and five or 3 per cent with three types. When the data are broken down, however, it is found that in the control group the mixtures were heterogeneous and consisted of almost any aggregation of the types encountered within the group. In the treated children, on the contrary, the mixtures were more uniform, running predominantly as combinations of types XI and XVIII, so that of the total 39 mixed cultures, 32 or about 80 per cent were of this category.

It may be of interest to introduce at this point a short comment on the possible source and persistence of the types encountered during this survey.

Since 1939, when epidemiological studies on acute respiratory infections were started by this laboratory at Letchworth Village, 23 cases of pneumococcal pneumonia occurred among the 60 children included in the present study. To expedite discussion of the cases, the pertinent details have been summarized in table 3. It will be seen that the 23 pneumonias were distributed among 20 children, since two (19 and 40) were afflicted three and

TABLE III

Previous Pneumococcal Pneumonias and Their Relation to Present (1942-1943) Carrier Types

Type during pneumonia	Number of child	Present group	Date of pneumonia	Recovery of homologous type	
				Same children	Other children
I	60	Treated	April 1941	Not recovered	Occasionally
	13	Untreated	March 1941	Not recovered	
	14	Untreated	March 1941	Consistently	
	19	Untreated	March 1941	Not recovered	
	37	Untreated	Jan 1942	Once	
IV	43	Treated	Sept 1939	Not recovered	Never
V	4	Treated	May 1941	Not recovered	Never
	58	Untreated	Oct 1941	Not recovered	
	5	Untreated	June 1941	Not recovered	
VI	1	Untreated	Jan 1941	Not recovered	Frequently
	3	Untreated	June 1941	Once	
	43	Treated	May 1941	Not recovered	
	10	Treated	Nov 1940	Not recovered	
VII	25	Treated	Dec 1941	Not recovered	Never
XI	40	Treated	April 1941	Consistently	Frequently
XI	29	Untreated	Oct 1939	Not recovered	Frequently
XIV	33	Treated	Dec 1941	Not recovered	Never
XVII	21	Untreated	May 1941	Not recovered	Rarely
XVIII	37	Treated	Nov. 1940	Not recovered	Frequently
XVIII	19	Untreated	Feb 1940	Once	Frequently
XIX	20	Untreated	April 1941	Not recovered	Rarely
XXII	15	Untreated	Oct 1941	Not recovered	Rarely
XXIII	19	Untreated	March 1940	Consistently	Occasionally (untreated group only)

Upon examination of the data for the incidence of the above types among the other children included in the study, it was found that types VI, XI and XVIII were present frequently, types I and XXIII, occasionally, types XVII, XIX and XXII, only rarely, while types IV, V, VII and XIV were never observed throughout the eight months of repeated typings. It appears, therefore, that the types found during the present survey cannot be entirely related with the previous pneumonias and that the distribution exhibits vagaries of types appearing in any large population.

*Reaction of types to sulfadiazine in vitro* An explanation for the curious predominance of the types in the nasopharynx of the treated children was readily obtainable when experiments were undertaken on the acquired resistance of the different types to sulfadiazine. In projecting this survey an effort was made to study (1) the susceptibility of the types occurring only

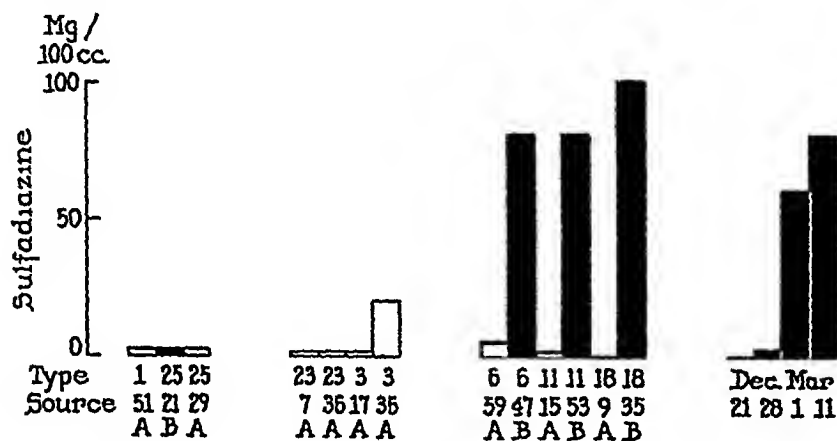


FIG 1 Resistance of pneumococcal strains to sulfadiazine. Black represents strains from treated group (B), white, from untreated group (A). Dated data on extreme right refer to type XI strains isolated at different times from the same treated individuals.

in the untreated children (e.g., types III and XXIII), (2) the susceptibility of types appearing sporadically in and disappearing abruptly from the throats of treated children (e.g., types I and XXV), and (3) the reaction of types encountered consistently in both groups (e.g., types VI, XI and XVIII).

In determining susceptibility, sulfadiazine was added to "pneumococcus broth" in varying concentrations, and inoculation of this medium and proper controls was accomplished with 0.5 c.c. of a 1:10 dilution of an 18 hour broth culture. Observations were recorded each day for three days. Since it was desired to acquire comparative figures, it was not felt necessary to seek the possibly greater accuracy obtainable with media free of sulfonamide-inhibiting substances. As a matter of fact, the results to be described were reproduced on several occasions within remarkable proximity.

In order to illustrate the nature of the results obtained, some of the data have been plotted in figure 1. Thus, in answer to the first question

implied above, two strains each of types III and XXIII recovered from different individuals of the untreated group were unable to tolerate completely as little as 2 mg. of sulfadiazine per 100 c.c., except for one strain of type III which did grow poorly at a concentration of 10 mg. Types as I and XXV, which appeared sporadically and disappeared quickly from the flora of treated children but persisted longer in the untreated children, were all highly susceptible. In no instance did they withstand more than 2 mg. of sulfadiazine per 100 c.c. Finally, the types occurring consistently in both groups (VI, XI and XVIII) were found to be susceptible (20 to 50 mg. per 100 c.c.) when isolated from untreated children, but appreciably resistant (80 to 100 mg. per 100 c.c.) when recovered from treated children. The evidence seems clear, therefore, that in prolonged administration of sulfadiazine, strains of pneumococcus may acquire an exalted degree of fastness to the drug.

However, in order to illustrate that the drug resistance might indeed be an acquired characteristic developing with continued application of sulfadiazine, an experiment was done to demonstrate this concept. Different cultures of the same type were isolated from the same individuals at successive intervals during the course of sulfadiazine treatment. Thus, a strain of type XI was isolated December 21, 10 days after treatment was begun. At this time, it was unable to grow in medium containing 1 mg. of sulfadiazine per 100 c.c. One week later (December 28) growth was observed in 2 mg. per 100 c.c. Approximately two months later (March 1) the organism grew in 60 mg. per 100 c.c., and 10 days later (March 11) the tolerance had increased to 80 mg. of drug per 100 c.c. (figure 1).

*Comparative virulence of strains and antibody titers.* Homologous types taken from both treated and untreated children were injected intraperitoneally in white mice in dilutions ranging from  $10^{-1}$  c.c. to  $10^{-8}$  c.c. of 18 hour broth cultures. The results revealed that irrespective of group derivation or of resistance to sulfadiazine, the strains of the same types were of the same degree of infectivity, suggesting not only a common source for the types in question, but, as has been pointed out by other workers, not even a loss in virulence or in serological specificity for strains refractory to sulfonamides. It is noteworthy that the virulence of all tested strains of type XI and XXIII was uniformly low for mice.

were also performed. In each test, the strains isolated from the children themselves were used as antigens. No antibody was detected by these means.

In this connection, it may be pertinent to mention observation on three children whose histories antedate the present study by two years. One of the children was given injections of type I specific carbohydrate<sup>3</sup> which rendered the skin reactive to the soluble specific substance but did not stimulate mouse protective antibodies. Within a year or less this child including two others not previously "immunized" suffered pneumonias due to pneumococcus type I. Following convalescence, all three possessed protective antibodies to a titer of 1000 lethal doses. Approximately two years after the pneumonias, or during the present study, antibody was again sought for but not detected by the reactions of agglutination, precipitation, *quellung* and protection.

TABLE IV  
Chronological Appearance of Type I Pneumococcus

Group	Child	Date of appearance								
		2/23 and before	3/5	3/15	3/25	4/19	5/10	5/20	5/31	6/10
Untreated	14	—	+	+	+	+	+	+	+	+
	28	—	+	—	—	—	—	—	—	—
	34	—	+	+	—	—	—	—	—	—
	37	—	+	—	—	—	—	—	—	—
	51	—	—	+	+	+	+	+	—	—
	7	—	—	—	—	—	—	+	+	+
	29	—	—	—	—	—	—	—	+	—
	39	—	—	—	—	—	—	—	+	—
	47	—	+	—	—	—	—	—	—	—
	22	—	—	—	—	—	+	—	—	—
Treated	49	—	—	—	—	—	+	+	+	—
	18	—	—	—	—	—	—	+	—	—
	40	—	—	—	—	—	—	—	+	—
	40	—	—	—	—	—	—	—	+	—

Line of separation in both groups divides the individuals carrying Type I during period of treatment from those detected after cessation of treatment.

*Incidence of type I* About two and one-half months after beginning drug administration, type I was abruptly encountered in the routine cultures. Never observed in the cultures preceding February 23, it appeared on March 5, the next date of culture, in four boys, all in the untreated group. The presence of this unusual carrier type can probably be explained by an outbreak of pneumonia due to type I pneumococcus in 1941, in the cottage housing the boys as described in earlier studies from this laboratory.<sup>1</sup> It seemed a good opportunity not only to chart its dissemination, but also to observe its infectivity among both treated and untreated children. The chronological course of the spreading is given in table 4. It will be seen that during the period of treatment it was recovered in five boys of the un-

treated and in only one of the treated group. Since the strain was found to be highly sensitive in vitro to the action of sulfadiazine (20 mg per 100 c.c.) the deduction, at first glance, is perhaps reasonable that the drug may have directed the distribution of the organism among the children. Moreover, following withdrawal of sulfadiazine, type I was found in five boys of the untreated and four boys of the treated group. In two of the untreated subjects (14 and 51) the organism persisted for several weeks, while in all others its appearance was transitory. Since this was true in both groups, it is difficult to believe that sulfadiazine per se was responsible for the transiency of this type.

*Distribution of types following treatment.* The data reviewed above suggest that with prolonged administration of sulfadiazine pneumococcal types become drug-fast and the more susceptible types tend to be elim-

TABLE V  
Distribution of Pneumococcal Types after Cessation of Treatment

Type of pneumococcus	Untreated group		Treated group	
	Number	Per cent	Number	Per cent
I	10	7.2	6	4.1
III	3	2.1	0	—
VI	38	27.1	38	27.5
IX	17	12.1	5	3.7
XI	11	10.0	18	13.0
XV	2	1.4	0	—
XVIII	27	19.3	32	23.2
XIX	3	2.1	0	—
XXII	0	—	3	2.2
XXIII	14	10.0	20	14.5
XXX	12	8.6	13	9.1
Totals	140	99.0	138	99.0

of which had never been recovered during the period of treatment. It is obvious that with cessation of drug there has been a marked tendency towards a broader distribution of types, and whereas some are still more frequent, the ratios are not so exaggerated as previously. The more generalized distribution of types with better approximation towards that occurring in the control subjects lends support to the belief that prolonged treatment has a restrictive influence on the incidence and distribution of pneumococcal types.

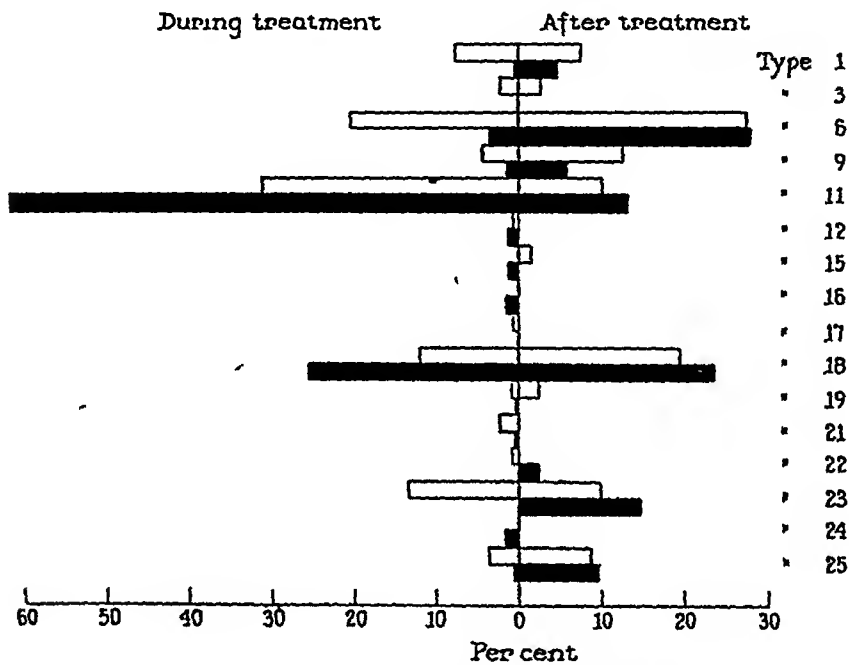


FIG 2 Distribution of pneumococcal types. Black represents strains from treated group (B), white, from untreated group (A).

Of equal interest in this connection is an analysis of the multiplicity of types found in the same individuals after the period of treatment. As the data summarized in table 6 reveal, mixed types were detected in the treated group 34 times, 26 times as dual types and eight times as triple types or

TABLE VI  
Occurrence of Multiple Types after Cessation of Treatment

Combination of	Untreated group			Treated group		
	Total	Types VI and VIII		Total	Types VI and VIII	
		Number	Per cent		Number	Per cent
Two types	29	3	10.3	26	6	23.1
Three types	7	1	14.3	8	4	50.0
Totals	36	4	11.1	34	10	26.5



more (i.e., on one occasion four types). Of the total mixtures, the combination of types XI and XVIII was found only 10 times (about 20 per cent) in the treated group. This is in sharp contrast to the incidence ob-

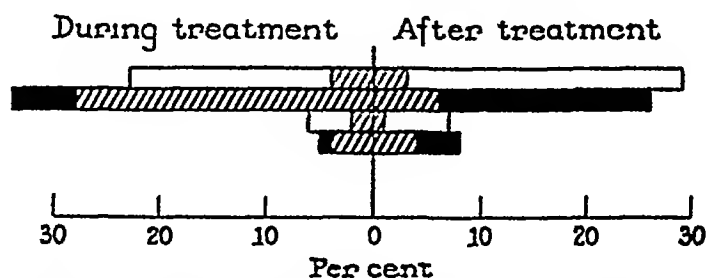


FIG. 3. Combinations of mixed pneumococcal types. Two upper bars represent a mixture of two types, lower bars, three types. Hatched gives mixture of types XI and XVIII; solid, mixture of other types. Black for treated and white for untreated group.

serviced previously of 32 times out of 39 (82 per cent) and it is more in line with observations on the diminution of these two types as sulfadiazine was withdrawn (figure 3).

plantation of pneumococci in the upper air passages. It may be that in some similar manner infection may be suppressed even by virulent strains already present in the tissues. The data suggest to the writers that except, perhaps, when promoted by poorly understood conditions as preëxisting morbidity, debilitation, lowered resistance, exposure, trauma, etc., pneumococcal infection is precipitated not by the individual's carrier types, but by types suddenly acquired from extraneous sources.

### SUMMARY AND CONCLUSIONS

1 Under prolonged sulfadiazine administration in physically normal children, pneumococcal types may acquire a high degree of resistance to the drug.

2 With resistance, there is a striking shift in predominance of types due to elimination of strains not so readily becoming fast.

3 Despite their fastness, the strains retain their virulence and specificity.

4 With discontinuation of drug treatment, the incidence of types tends towards a more normal distribution.

5 Precipitating, agglutinating and protective antibodies were not found in either treated or untreated children.

6 Lack of clinical infection by virulent carrier types was frequently unrelated to either drug treatment or detectable circulating antibody.

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# NOTES ON 250 CASES OF SUBACUTE BACTERIAL (STREPTOCOCCAL) ENDOCARDITIS STUDIED AND TREATED BETWEEN 1927 AND 1939 \*

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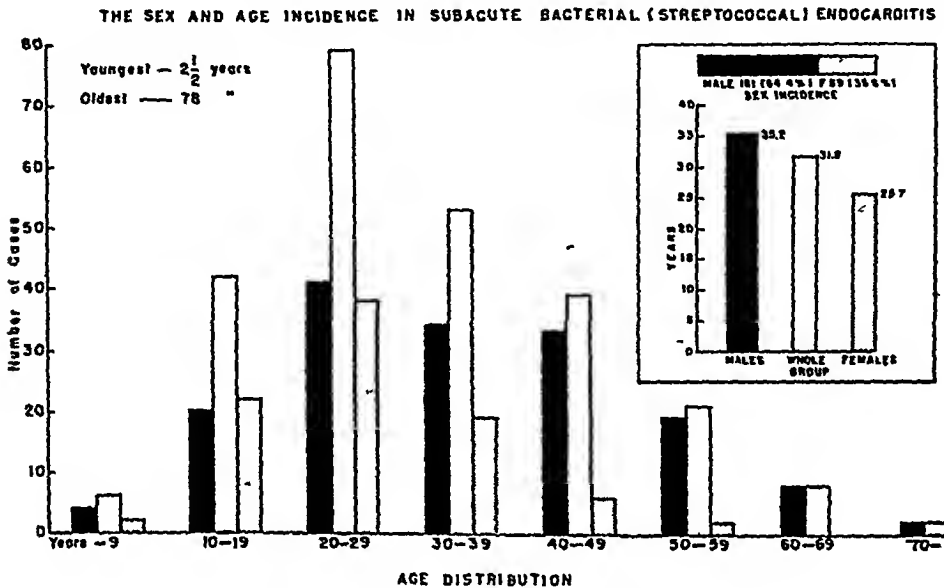
IN order to understand more fully the clinical picture of subacute bacterial (streptococcal) endocarditis,<sup>†</sup> to determine the effects of treatment prior to the intensive use of the newer chemotherapeutic drugs, and to establish a baseline of prognosis particularly as a means of evaluating therapy, we have analyzed the records of 250 patients with this disease in certain Boston hospitals  $\lambda$  and in private practice  $\S$  from January 1927 to March 1939.

Although excellent reviews of this disease have been published in the past and collections of cases assembled, as in the writings of Libman and Friedberg,<sup>1</sup> Blumer,<sup>2</sup> Morrison,<sup>3</sup> and Christian,<sup>4</sup> it was thought necessary to cover the years immediately prior to 1939 with a large enough series of cases studied in one community for adequate comparison with clinical findings and therapeutic results in that same or similar environment since 1939.

Such an analysis should guide us reliably as to the outlook for the definitely diagnosed case of this infection as seen in the days before the newer chemotherapy, although we agree that there may be a different prognosis in certain mild and usually clinically undetectable instances of the disease; we have *not* included any such cases in the present analysis because of their uncertainty.

The great majority of the present series of 250 patients had rheumatic valvular disease as a background, a few had congenital defect, including five instances of patency of the ductus arteriosus. Only clinically definite cases were included in this study, all had cultures positive for the non-hemolytic streptococcus, either of the alpha (viridans), or rarely, the gamma

(anhemolytic) variety In this series of patients there were 161 males (64.4 per cent) and 89 females (35.6 per cent) The average ages of males (35.2 years) and females (25.7 years) and of the group as a whole (31.8 years) and the distribution of patients according to age are noted in chart 1 The youngest patient was two and one-half years of age and the oldest was 78



## PART I—DIAGNOSIS AND CLINICAL RELATIONSHIPS

*The Clinical Picture* Subacute bacterial endocarditis presents a remarkably varied clinical picture, with signs and symptoms changing with the manifestations of the three underlying processes—infection, embolism, and intrinsic cardiac damage. The disease may begin mildly, with irregular progression of disability due chiefly to the infection itself, resulting in increasing malaise, fever, pallor, and anorexia. It may arise suddenly, with the occurrence of an embolism while the patient has been in apparently good health (though close questioning will disclose, as a rule, a preceding period of at least slight malaise). At times—as in some cases following tooth extraction—the infectious factor may be intense from the start, with chills and high spiking fever. Nearly always, however, these two elements, infection and embolism, mix, with embolism complicating and aggravating the course of infection. The third factor, that of intrinsic cardiac damage, relates both to the preëxisting cardiopathy and to the changing heart lesions of the present illness, the systemic infection, resulting in fever, anemia, and at times nutritional deficiency, reacts upon the heart, which itself may be attacked also by embolism. Changing heart murmurs, increase in heart size, and the common occurrence of varying degrees of failure are the principal manifestations of this third underlying process.

Chart 2 presents the frequency of certain salient clinical features of subacute bacterial (streptococcal) endocarditis. The percentage of incidence of heart murmurs refers to the findings at the time of entrance into the hospital, murmurs developed later in the only two patients in whom they were not heard on admission. The percentage of the other findings is based on their incidence over the period of known observation—during the hospital stay, and—so far as information could be obtained—before and after that time. The incidence of these clinical features would have been found to be greater, of course, if careful observation had been recorded over the entire length of the illness. Splenomegaly, clubbing of the fingers, and petechiae (along with heart murmurs and fever, both present in the course of every case studied) have been considered the most typical findings of the disease. The triad was found to be present in 13.1 per cent of the patients, 6.1 per cent showed none of the three.

*Differential Diagnosis.* A large number of diseases figure in the differential diagnosis of subacute bacterial endocarditis. These conditions, as they were considered in the present series of cases, are tabulated below.

#### *More Commonly*

Grippe	Subarachnoid hemorrhage
Rheumatic fever	Brain tumor
Renal calculus	Brain abscess
Meningococcus meningitis	Cerebral hemorrhage
"Pleurisy"	Central nervous system syphilis
Pulmonary tuberculosis	Latent syphilis
Pneumonia	"Angina pectoris"

#### *Less Commonly*

the bacterial endocarditis could not be learned. Malaise, pallor, and elevation of temperature in these patients with heart murmurs and commonly with histories of rheumatic infection in the past, repeatedly suggested rheumatic fever. In view of the great frequency of cerebral embolism in sub-

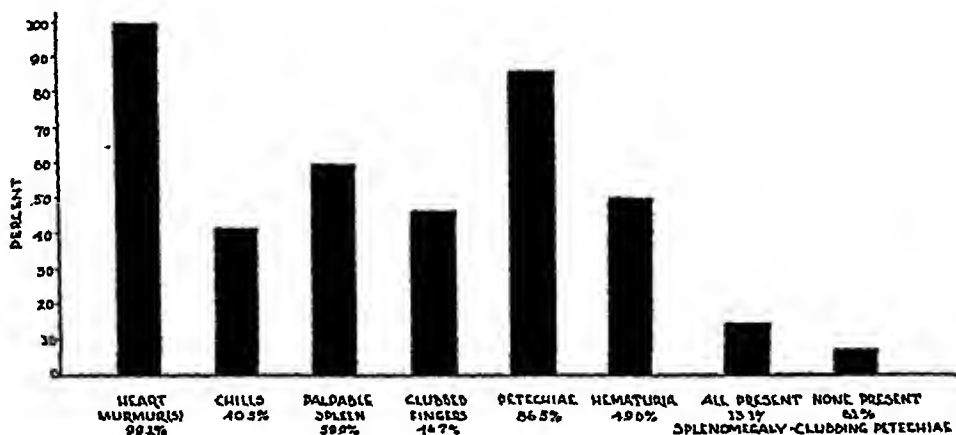


CHART 2 The incidence of certain salient clinical features in 250 cases of subacute bacterial (streptococcal) endocarditis

acute bacterial endocarditis, it is not surprising that intracranial diseases should appear so prominently on the list.\* In one case the right cerebellum of a patient was operated upon in futile search for an abscess. The diagnosis of pneumonia was made often because of the occurrence of chills and fever. Pain resulting from splenic infarction frequently prompted a diagnosis of "pleurisy." Costovertebral pain and hematuria suggested renal calculus. Intra-abdominal embolism led to the diagnosis of an acute surgical emergency: in five instances appendectomies were performed, in one a cholecystectomy, and in another a laparotomy was done for a suspected perforated peptic ulcer. "Fever of unknown origin" was commonly diagnosed, and search made for undulant fever, typhoid, subphrenic abscess, portal thrombophlebitis, etc.† In one striking instance, the lung fields were so studded with infarcts in a patient whose infection complicated patency of

\* Syphilis of the central nervous system and elsewhere was diagnosed as the primary disease or as an accompanying condition because of falsely positive serological tests. Without histories or definite signs of syphilitic infection patients gave positive tests, but at autopsy presented no lesions of syphilis; such tests are most misleading in those with aortic regurgitation without previous known rheumatic fever or chorea. Two particularly interesting later cases—with underlying heart disease of known rheumatic etiology—showed positive serological tests on admission (in one, a blood test had been negative shortly before the present illness), which became negative after apparent recovery from subacute bacterial (streptococcal) endocarditis following sulfapyridine-heparin therapy.

† A recent case, seen by one of us (S. R. K.) subsequent to the present series at first had been diagnosed and treated as malaria. The chills and fever, anemia, and splenomegaly of bacterial endocarditis may readily suggest malaria, and the heart murmur may be thought related to the anemia and fever. With the greatly increased present and expected incidence of malaria as brought from distant battlefronts, this disease will assume more importance in the differential diagnosis.

the ductus arteriosus that a roentgen-ray diagnosis of miliary tuberculosis was made. The amenorrhea often accompanying bacterial endocarditis caused the suspicion of pregnancy in two patients, indeed, one woman with severe heart disease had been sent into the hospital for a therapeutic abortion.

Delay in taking or in repeating blood cultures was the chief factor in delaying recognition of the true nature of the patient's illness. It is an important rule that *fever and malaise in an individual with a heart murmur*

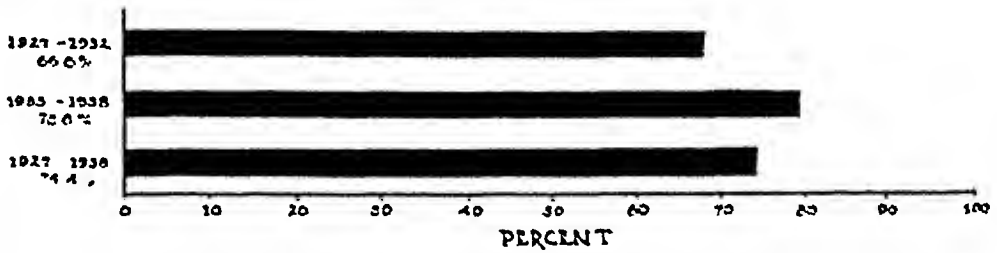


CHART 3 Incidence of positive blood cultures in all cultures taken in proved cases of subacute bacterial (streptococcal) endocarditis

dental procedures Okell and Elliott<sup>6</sup> found that multiple extractions in cases with marked gum disease were followed by bacteremia in 75 per cent of the instances, single or multiple extractions led to bacteremia in 34 per cent of the cases in which no gingival disease was apparent \* Merely rocking a tooth in an infected gum could discharge bacteria into the blood<sup>7</sup> In persons with preëxistent valvular or congenital heart disease such organisms usually disappear from the blood quickly and without harmful effect (as in those with normal hearts), but they may implant in crevices of the endocardium, become surrounded with platelets and fibrin, and establish bacterial endocarditis The following statements are taken from six of the case records in the present series

"Ulcerated molar extracted, followed by chills and fever"

"Five teeth pulled, chills occurred a few days later"

"Two teeth removed before onset, anorexia and then joint pains followed directly"

"One week before onset, 10 bad teeth removed, pus found in sockets"

"Tooth removed before onset (two weeks later), much digging for retained root"

"Ten remaining teeth removed while patient was in excellent health, one week later, drenching sweats, chills, and fever occurred"

These are striking examples, but other charts mention single uncomplicated extractions preceding the onset of the present illness Many records also note extensive untreated dental disease, which is likewise hazardous with such oral sepsis, *Streptococcus viridans* occurs in greatest numbers, and readily enters the blood stream, even in the absence of operative interference<sup>8</sup>

The frequency of dental work as the predisposing cause of subacute bacterial (streptococcal) endocarditis cannot be determined from the present study because the problem was not specifically investigated in many instances in the history-taking, after looking into the question in a larger series of patients personally seen, one of us (S R K) estimates that in approximately one case in four the disease follows some dental procedure For persons with known rheumatic or congenital heart lesions, or at times even with murmurs which have been thought to be physiological ("functional"), tooth extractions, less severe dentistry, and untreated oral sepsis carry a definite serious risk<sup>1</sup> For them these warnings are urgent

- 1 Take scrupulous care of the teeth, treat minor disturbances as they come, to avoid major dental procedures
- 2 Avoid extractions unless clearly warranted, let no teeth be red, used as possible foci of infection for systemic disease unless definite endocarditis is found

\* These cultures usually were taken when the patient was under general anesthesia. It is pointed out<sup>9</sup> that the incidence of post-extraction bacteremia has been found lower, being about 17 per cent when local anesthetics are used perhaps because of the vasoconstrictive action of adrenalin contained in the solutions



3. Avoid harsh or heroic dentistry, not too much attempted at one time and as little trauma as possible.

There is evidence that the use of sulfonamides may prevent or reduce the frequent occurrence of bacteremia after tooth extractions,<sup>8, 9, 10</sup> but further well-controlled studies on large series of patients are needed to determine the value and preferred technique of such medication. At present, it seems desirable to administer a sulfonamide drug active against the *Streptococcus viridans* to those with rheumatic or congenital heart disease at the time of dental extraction. Sulfadiazine, with equal amounts of sodium bicarbonate, begun approximately 10 hours before the planned extraction, with an initial dose of two grams by mouth, followed by four one-gram doses at intervals of four hours is a recommended schedule. With this the risk of toxic effect is slight, as is the likelihood that if the disease should nevertheless occur the sulfadiazine will have produced resistance to the action of sulfapyridine (the sulfonamide drug of choice in therapy) on the organisms.\*

The onset of subacute bacterial endocarditis was preceded in seven instances by trauma: an automobile injury with severe bruising of the side of the body, an automobile injury resulting in the fracture of a rib, lifting a motorcycle, which caused the side "to go dead", a fall to a concrete floor 12 feet below, stepping on a nail, with swelling of the foot, which required incision, a fracture of an ankle, a fracture of the skull, with surgical excavation of the clot. The possible causal linkage in these instances is very difficult to evaluate. In each, the accident occurred at a time of usual good health, the frequent mild onset of the disease makes careful questioning concerning the previous state of health extremely important. No other

infection or dental procedure to which the disease could be ascribed intervened. In most instances, however, no definite source of the disease can be discovered. Penetrating injuries, such as the punctured foot and fractured skull, provide stronger argument for direct causal relationship, but it is likely that even non-penetrating wounds, with or without obvious inflammation, may set off the crucial transient blood-stream invasion of so common a saprophyte as the non-hemolytic streptococcus. More extensive studies of the varieties and degrees of severity of conditions under which these invasions may occur would help to solve this perplexing problem. Meanwhile, the following hypothesis seems just: injuries occurring when the presence of infection can be excluded by careful history-taking, and followed (without the intervention of known etiological factors such as dental extractions) within a reasonable period (one month would seem a fair limit) by evidence of bacterial endocarditis, may be considered presumptive causative factors in the disease.

*Concurrence of Subacute Bacterial Endocarditis and Rheumatic Fever*  
Views of the relationship between subacute bacterial endocarditis and rheumatic fever have varied widely. Von Glahn and Pappenheimer<sup>12</sup> concluded that, "active rheumatic vegetations are, in persons who have had rheumatism, a necessary and practically constant prerequisite for the implantation of bacteria." Levine,<sup>13</sup> however, writes "These differences in skin reactions and other suggestive clinical evidences of a certain incompatibility between the rheumatic state and bacterial endocarditis, have led me to think that those individuals who lose their rheumatic predisposition or allergic type of response are the ones who become more susceptible to the development of bacterial endocarditis. The more immune they become to the one, the more susceptible to the other." Other writers have believed that both infections are manifestations of one disease, and that subacute bacterial endocarditis is a virulent form of rheumatic fever.<sup>14</sup>

Among the cases studied, the coexistence of the two diseases has been diagnosed clinically and confirmed at autopsy. Two types of relationship appear to be present.

(1) Subacute bacterial endocarditis may act as a specific or non-specific factor to activate rheumatic fever in susceptible subjects, as tonsillitis, upper respiratory infections, sunburn, trauma, etc., may do. The following case illustrates such an association of the two diseases.\*

A man of 22 (E. S.), who had had five attacks of rheumatic fever resulting in great heart damage, showed characteristic findings of subacute bacterial endocarditis with four blood cultures positive for *Streptococcus viridans*. Because of a red tender joint, prolonged auriculoventricular conduction time, and epistaxes, concurrent rheumatic fever was diagnosed and further indicated by the appearance of auricular fibrillation. All evidences of subacute bacterial endocarditis disappeared after sulpiridine-heparin therapy, 19 consecutive blood cultures were negative. Slight fever and progressive congestive heart failure, however, pointed to continuing rheumatic

\*This and the following case were studied after the original group of 250

infection. He died in anasarca six months after specific therapy was completed. Autopsy showed an area of clear-cut, definitely healed bacterial endocarditis consisting of typical vegetations, fibrosed and calcified, on the chronically scarred (rheumatic) mitral valve. Cultures, smears, and sections revealed no bacteria. Numerous Aschoff bodies were found in the myocardium.

The following findings in the course of bacterial endocarditis point to concomitant rheumatic fever:

- 1 Tender, swollen joints
- 2 Prolonged auriculoventricular conduction time
- 3 Epistaxis
- 4 Auricular fibrillation

(2) Subacute bacterial endocarditis may occur during the course of rheumatic fever. In the following case, as in some others of this group, the superimposed bacterial infection appears related to dental extraction.

Pallor, fever, leukocytosis, elevated sedimentation rate, subcutaneous nodules and signs of developing mitral and aortic valvular disease established the diagnosis of typical rheumatic fever in this six year old boy (R. DeS.). Eight months after the onset of this illness, an aching, decayed tooth was extracted. One month later chills and high swinging fever occurred, and soon petechiae, splenomegaly, and cultures positive for non-hemolytic streptococci were found. Autopsy two months later showed chronic rheumatic mitral and aortic disease, active rheumatic myocarditis and endocarditis, and the lesion of bacterial endocarditis on the left auricular wall.

The following findings in the course of rheumatic fever point to superimposed bacterial endocarditis:

- 1 Chills
- 2 Visceral emboli
- 3 Osler nodes
- 4 Repeatedly positive blood culture
- 5 Splenomegaly

diagnosed clinically, postmortem examination showed actual chronic stenosis to be present only three times, in all five instances in which the diagnosis had been questioned, stenosis was absent, it was present in the two cases in which the diagnosis had been made in conjunction with that of aortic stenosis

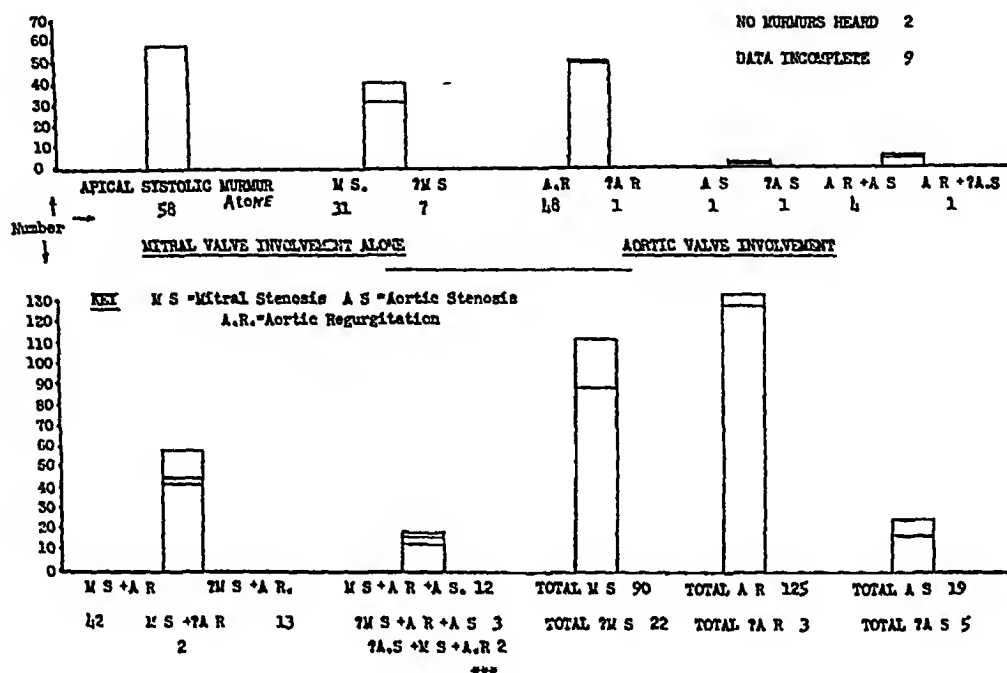


CHART 4 The underlying cardiac lesions in 250 cases of subacute bacterial endocarditis clinical findings

TABLE I

The Diagnosis of Rheumatic Mitral Stenosis in Subacute Bacterial Endocarditis

Clinical Findings			Pathological Findings					
Diagnosis	No	With Aortic Diastolic Murmur	Mitral Stenosis	Mitral Disease (Rheumatic) without Stenosis	Bacterial Vegetations (Mitral)	Mycotic Aneurysm	Perforated Valve Cusp	Normal Valve
Mitral stenosis	19	10	3	10	19	1	3	0
?Mitral stenosis	5	5	0	3	4	1	0	1
?Mitral stenosis ?Austin Flint murmur	1	1	0	0	0	0	0	1
Mitral and aortic stenosis	2	2	2	—	2	0	0	0
No mitral stenosis	30	—	1	—	—	—	—	—

The apical diastolic murmurs which had led to the mistaken clinical diagnosis of rheumatic mitral stenosis were caused, it is believed, by the bacterial vegetations, by aneurysm or perforation of the valvular cusps, or by dilatation of the left ventricle from anemia, infection, and perhaps nutritional disturbance giving relative mitral stenosis (the probable Austin Flint mechanism) \*. In some cases, aortic regurgitation itself was an important factor. Unless the mitral diastolic murmur is known to have been present *prior to* the bacterial infection and the diagnosis of mitral stenosis then made, it is best to speak only of "mitral disease." Even this diagnosis, however, may then be incorrect, for occasionally patients with mitral diastolic murmurs have shown at autopsy mitral valves free of both rheumatic and bacterial lesions, the dilatation of the left ventricle incident to the present illness (with vegetations on the aortic valve producing or aggravating regurgitation through it) causes a relative mitral stenosis capable of producing the murmur. Overlooking an organic mitral stenosis—an error opposite to that discussed above—occurred but rarely in this series, in 30 of the instances in which mitral stenosis had not been diagnosed it was found at autopsy in only one.

In the presence of aortic regurgitation, apical *systolic* murmurs heard during the course of bacterial endocarditis can not be interpreted as conclusive evidence of mitral disease, either rheumatic or bacterial. The finding of a loud apical systolic murmur prior to the present illness would point to an organic mitral regurgitation, otherwise, the murmur may denote regurgitation through a structurally normal valve. If there has been previous injury to the mitral valve, bacterial vegetations quite regularly localize there. Of 44 patients showing lesions of the mitral valve at autopsy, with scarring or vegetations or both, only two presented a scarred valve which was free of vegetations. In the other 42 patients, in whom the mitral valve was a site of bacterial implantation, it was described as showing no evidence of old impairment in three, the heart appeared to have been normal in two of these, and in the third showed patency of the ductus arteriosus and slight coarctation of the aorta.

Among 32 autopsied cases which had shown aortic diastolic murmurs, only two failed to present the lesions of bacterial endocarditis on the aortic valve, one of the two showed a chronically scarred and the other a normal valve. In seven other cases, six with postmortem findings of bacterial vegetations on the aortic valve and one with chronic aortic valvular disease.

\* It is interesting that in seven of the patients, subsequent to this present series, apparently cured of subacute bacterial endocarditis following sulfapyridine-heparin treatment,<sup>10</sup> apical diastolic murmurs have been found to disappear, both in those with aortic regurgitation and those without it. Alterations in the vegetations in the process of healing, and decrease in size of a previously dilated left ventricle have been considered the explanation for this regression of signs. In five of the successfully-treated patients, also, a high-pitched, musical ("sea-gull") systolic murmur arose at the apex or near it during the course of therapy and later disappeared, it occurred in only one of the cases in which treatment failed, a patient who had shown marked initial improvement.

without vegetations, no aortic diastolic murmur had been heard\* (In only two cases—one with and one without an aortic diastolic murmur—of the autopsied 38 showing aortic valvular involvement, with chronic scarring or bacterial vegetations or both, was a scarred aortic valve found free of vegetations) In the four autopsied cases in which aortic stenosis had been diagnosed, chronic stenosis was found pathologically in all, it was present, but had not been detected clinically, in two more Bacterial vegetations described as nearly occluding the valvular orifice had not led to a clinical diagnosis of aortic stenosis in two other cases

An aortic diastolic murmur heard in a patient with subacute bacterial endocarditis does not necessarily indicate an antecedent aortic regurgitation Unless the signs of this lesion were found prior to the present illness, such a murmur may result from bacterial vegetations implanted upon a valve scarred insufficiently to have permitted regurgitation, or, as described in four of the present cases, upon a normal valve Since less severe damage will produce regurgitation than is needed to cause stenosis of a valve, the erroneous diagnosis of chronic aortic regurgitation on the basis of a diastolic murmur will be proportionately less common than that of mitral stenosis The aortic diastolic murmur in cases with subacute bacterial endocarditis, as noted above, is a quite reliable indication that vegetations are present on the aortic valve

## PART II—PROGNOSIS AND THERAPY

Of the 250 cases studied, 246 could be adequately followed up None of these survived long, but in one instance there was a cessation of findings referable to subacute bacterial endocarditis, and death was due to rheumatic myocarditis 13 months after the diagnosis of bacterial endocarditis had been made In this series of cases, this patient, who had received no specific therapy, was the sole instance of apparent recovery, but it is possible that he should not have been included in the series at all, thus the only possible recovery of the entire lot was himself, a somewhat doubtful case to start with His record follows

*B D N* was found to have heart disease at the age of 17, six months before his first admission to the Massachusetts General Hospital (on March 19 1928) with the chief complaint of shortness of breath on slight exertion The diagnosis of rheumatic fever was made, with mitral stenosis and regurgitation and aortic regurgitation the presence of adherent pericardium was suspected After discharge he remained in bed for six weeks, in bed and chair for 14 months, and was then up and about and capable of moderate exertion while receiving digitalis, despite signs of rheumatic activity from time to time

Three days before his second hospital admission (on October 27 1930) he became aware of sudden severe palpitation, and had slight fever and cough The

\* It is possible that in one of these cases, one with a patent ductus arteriosus and slight coarctation of the aorta already mentioned, vegetations on the aortic valve gave rise to a diastolic murmur which was obscured by that resulting from patency of the ductus Vegetations on the aortic valve, like those on the mitral were implanted in this instance upon a valve apparently normal previously

electrocardiogram showed auricular fibrillation. Two of four blood cultures were positive for *Streptococcus viridans*, there were repeated crops of petechiae, a splinter hemorrhage, low-grade fever to 100.8° F by rectum, splenomegaly, 1-2 red blood cells per high power field in the urine, but no anemia or clubbing of the fingers. The diagnosis of subacute bacterial endocarditis was made. The patient was discharged November 20, 1930 to the Beth Israel Hospital, where he gained weight, had no rise in temperature over 99° F by mouth, and showed no further petechiae. All six blood cultures taken there showed no growth. He did have three attacks of sharp left upper quadrant pain, however, which suggested splenic infarction.

At home, on a restricted regime, the patient had no complaints until four weeks before his third admission to the Massachusetts General Hospital (on June 24, 1931) when he suffered from epigastric pain, nausea, vomiting, dyspnea, cough, and nocturia. On admission he was dyspneic and showed mild icterus, slight cyanosis, and a definite Broadbent's sign, but no petechiae or fever. Two blood cultures were negative. The urine showed a few red blood cells, a slight to a large trace of albumin, and a few granular and hyaline casts. Blood non-protein nitrogen was 42 mg per cent. After returning home, the patient suffered from dyspnea, palpitation and nervousness, and six weeks before his fourth admission (on November 19, 1931) he felt a severe constricting precordial pain lasting one hour. Two weeks before admission, he had great dyspnea, palpitation, and precordial pain. He coughed up blood-tinged sputum. The findings of tachycardia (difficult to control with digitalis), nervousness, weight loss, diarrhea, hot skin, stare, slight exophthalmos, and inability to shut his eyes suggested thyrotoxicosis, the basal metabolic rate was plus 26 per cent. There was no response to iodine, however, and the diagnosis was rejected. Aortic stenosis was now found to be present. Two blood cultures were negative, the urine showed a trace of albumin, and was loaded with hyaline and granular casts, the red blood count was 5,000,000. The patient died rather suddenly on December 10, 1931 in an attack of severe palpitation, tachycardia, cyanosis, and dyspnea.

At *postmortem examination*, the heart weighed 875 grams, and showed acute and chronic rheumatic endocarditis of the mitral, aortic, and tricuspid valves, with mitral and aortic stenosis and insufficiency and tricuspid insufficiency. The myocardium contained Aschoff bodies. There was a thick yellowish nodule 3-4 mm in diameter on the sinus side of the right posterior aortic cusp, and a "deposit of relatively thick grayish nodules along the line of closure of the tricuspid valve." These nodules were not sectioned, but the latter nodules appeared identical with nodules studding the pericardium, which on microscopic examination showed dense hyaline material. The spleen was greatly enlarged, weighing 310 grams. There was chronic adhesive pericarditis, with fibrous pleuritis, and general chronic passive congestion. The kidneys showed moderate fibrous intimal thickening of the arterioles, and, rather uniformly throughout, some hyalinization of glomerular tufts, proliferation of the endothelial lining of glomerular capillaries, and moderate congestion. An occasional glomerulus showed capsular proliferation.

The diagnosis of subacute bacterial endocarditis here was made at the time of the second hospital admission on the basis of valvular heart disease, two positive blood cultures, petechiae, a splinter hemorrhage, splenomegaly, microscopic hematuria, and slight fever. From the time of discharge from this hospital stay until his death, a little more than one year later, the patient showed no further evidence of the disease. The finding at autopsy of firm nodules on the aortic and tricuspid valves is consistent with but not proof of the diagnosis of a healed bacterial endocarditis, these nodules were not studied microscopically, and may perhaps have contained bacteria. Such

a diagnosis, therefore, though indicated clinically, cannot be considered as certain pathologically, it is possible that the infection may have become only quiescent\*. During the course of the review one other case seemed on superficial study to belong to the rare recoveries, but careful analysis forced its exclusion as an authentic instance of subacute bacterial endocarditis.

Intervals of normal temperature lasting as long as one week were common in the present series of cases, but afebrile periods of one month (after fever had once risen and the disease was clearly present) were rare, and no patient with this extended normal temperature, except the patient noted above, was free of signs and symptoms of the disease during so long a period of time.

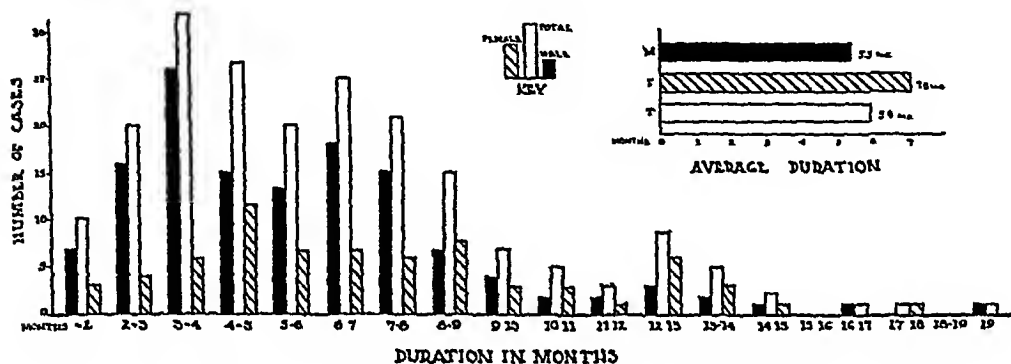


CHART 5 The duration of infection in subacute bacterial (streptococcal) endocarditis

Uncertainty as to the time of the onset makes difficult a determination of the length of the infection, for in many instances the disease at first pursues a very mild course. In as far as possible, the duration has been reckoned from the onset of malaise. Chart 5 shows the average duration for males and females and for the whole group, and apportions the cases according to the number of months of survival. The numerically largest group survived three to four months, the second largest four to five months. The longest duration of infection in any instance was 19 months. The distinct difference in the duration in females, with an average of seven months, from that of males, with an average of 5.3 months, is puzzling. The younger average age of the female victims (25.7 years) as compared with the average age of the males (35.2 years) may be a factor in this discrepancy.

**Treatment, 1927-1939** In few, if any, other diseases have such a number and diversity of treatments been attempted as in subacute bacterial endocarditis. These various methods, with the number of instances of their use, are recorded in table 2. Except for the newer chemotherapeutic drugs

\* Particularly the splenomegaly and renal changes found at autopsy raise the possibility here of the "bacteria-free stage" of the disease, as described by Libman.<sup>1</sup> The lack of brown pigmentation of the face and especially the absence of anemia, among other features make this interpretation very unlikely.



TABLE II

Forms of Therapy Used in Subacute Bacterial (Streptococcal) Endocarditis, Study of 250  
 \* Patients Treated January 1927—March 1939

BIOLOGICAL		DRUG	
<i>Transfusions</i>		<i>Chemotherapeutic</i>	
Whole Blood Transfusions	45 Patients	Sulfarsonal	1
From Immunized Donors	3	Phenyl Mercuric Nitrate	2
From "Recovered" Patient	1	Quinine Compound	1
		Bismuth Tartrate	1
<i>Bacteriophage</i>		Neoarsphenamine	2
Alone	7	Sodium Cacodylate	4
In Combination with Acriflavine	1	Carbolic Acid	1
		Metaphen	2
<i>Vaccines</i>		Acriflavine	2
Autogenous	9	Gentian Violet	3
Stock	2	Mercurochrome	3
B C G	1	Prontosil	5
		Sulfanilamide	24
<i>Sera</i>		Sulfapyridine	4
Streptococcus Lysate (Lilly)	1		
Antistreptococcal Serum (Parke-Davis)	1	<i>Non-specific</i>	
Polyvalent Antistreptococcal Serum	1	Peptone Solution (1 v )	1
Scarlet Fever Streptococcal Antitoxin	1	Sterile Milk (1 m )	2
Antistreptococcal Horse Serum	2	Turpentine (1 m )	2
Antistreptococcal Goat Serum } (Foshay)	1		
Antimeningococcal Serum	1	<i>Miscellaneous</i>	
		Sodium Nucleinate	1
<i>Inoculation with Living Organisms</i>		Spleen Marrow	1
<i>Str viridans</i> from the Patient's Blood	5	Cysteine	1
Malaria—Injections of Infected Blood	1	Salyrgan	1
Rat-Bite Fever—Injection of Blood from Guinea-Pig Infected with <i>Spirocheta morsus-muris</i>	1		
PHYSICAL			
Hyperthermia			1
Ultraviolet Radiation			2
Radiotherapy over Heart			3
Sunlamp			4
SURGICAL			
Attempt to Obliterate Infected Patent Ductus Arteriosus			1
Cautery of Deep Fascia of Chest Wall			1
Tonsillectomy			4
Tooth Extraction			11
SYMPTOMATIC AND GENERAL			
This includes the administration of opiates, iron, salicylates, digitalis, high caloric diets, vitamins, etc		Many	

these agents produced only slight temporary improvement, or, far oftener, none at all. Frequently they increased discomfort and hastened death, chills, heightened fever, nausea, vomiting, burns, abscesses, deafness, and prostration were among their toxic effects. In some instances, transfusions of whole blood helped, particularly in patients with severe anemia. Immunotransfusions were not superior. After the withdrawal of 1000 c c of blood from one of the three patients treated by this method,<sup>16</sup> she was given a single transfusion of 1800 c c of blood from three donors immunized with killed

cultures of her organisms. In the next 15 weeks she received five more 500 c c immunotransfusions, but the treatment did not change the course of the disease. Agglutination tests on the blood of the patient and donors showed that the patient possessed a higher titer of antibodies than any of the donors. Many investigators<sup>19, 20, 21</sup> have demonstrated the almost constant presence of antibodies, both agglutinins and complement-fixing bodies, for the patient's own and homologous organisms, in the blood of those with bacterial endocarditis\*. The occurrence of this antibacterial power in the patient's own blood points to the futility of biological and non-specific drug therapy intended to add to or to stimulate the production of immune bodies in the blood. These considerations apply strongly to the transfusion of blood from donors recovered from *Streptococcus viridans* infections, a measure which the many frantic and pathetic appeals by radio and newspaper have publicized as the sole chance for sufferers from subacute bacterial endocarditis. Besides raising hope falsely in the families of these patients, such appeals render them prey to very dubious "recovered" donors, led more by financial than humanitarian desires.<sup>23</sup>

The one patient who received an injection of guinea-pig blood infected with the *Spinocheta morsus-muris* developed symptoms of rat-bite fever so alarming that specific therapy had to be administered against this disease, but when it had been controlled, the bacterial endocarditis remained.

In one instance, a bold surgical treatment was attempted, the ligation of an infected patent ductus arteriosus. Because of strong adhesions between the ductus and the right pulmonary artery, successful closure was impossible. The patient died four days later, and autopsy showed vegetations at the pulmonary orifice of the ductus, and growing extensively on the wall of the pulmonary artery below. In a report of this case,<sup>24</sup> the authors stated their belief that such therapy can succeed only when vegetations are confined to the ductus and its immediate vicinity, they found in the literature however, only a single instance in which these were limited to the pulmonary orifice of the ductus, and only a few in which the lesions were restricted to the ductus and the pulmonary artery. Despite this earlier failure, Touroff, guided by the pioneer work of Gross<sup>25</sup> in ligating the non-infected ductus, was able to report in 1940 the surgical closure of an infected patent ductus arteriosus, with recovery from subacute bacterial endarteritis.<sup>26</sup> This operation, also performed early and with success by Keele in England in a case of influenzal endarteritis,<sup>27</sup> has resulted in numerous apparent cures reported by several workers †

\* Poston and Organ,<sup>22</sup> however, could demonstrate "no significant serologic evidence of immunity" "in the active bacteremic stage of bacterial endocarditis" among eight patients five of whom were infected with *S. viridans*. In some of these patients immune bodies appeared or increased with the disappearance of bacteremia.

† Touroff<sup>26</sup> believes that surgical closure of the patent ductus arteriosus overcomes the infection by (a) preventing the entrance into the aorta of infective material arising from the pulmonary side of the ligature, and allowing it to pass only into the pulmonary artery, (b) preventing traumatization of vegetations within the ductus and pulmonary artery by the strong aortic current, thus reducing the amount of infective material swept into the pul-

Removal of tonsils and teeth, even though heavily infected, proved futile. With the bacteria implanted in the endocardial vegetations, it is hard to imagine how removing such foci, even though they may have been the original source of infection, can cure. One of us (S. R. K.)<sup>33</sup> has seen a second attack of subacute bacterial endocarditis follow directly the extraction of two abscessed teeth, in a patient apparently cured by one of the newer methods of therapy (sulfapyridine and heparin), the importance of eradicating foci of possible reinfection *before* beginning treatment has therefore been stressed. The most imaginative method of treatment noted was perhaps the use of salyrgan, "to dehydrate the patient to render the environment less favorable to the organisms." Although no patients underwent therapeutic splenectomy, it is interesting to note that the disease occurred and followed its usual course in one patient whose spleen had been removed five years earlier because of Gaucher's disease.

Of the general methods of therapy, the use of large doses of vitamin C has particular significance, in view of the importance of this vitamin for effective wound healing<sup>34, 35</sup> and the demonstration of its deficiency in patients with prolonged infections.<sup>36</sup>

The use of specific drug therapy showed no noteworthy effect on the course of the disease prior to the introduction of the sulfonamides. No definite improvement was observed in the five patients who received Pron-tosil, but the use of sulfanilamide in 24 cases was followed by lowered temperatures in five patients and by negative blood cultures in two. Among the four cases in which sulfapyridine was used, it appeared more effective than sulfanilamide in reducing the temperature, two patients showed negative cultures for a time, but none derived prolonged benefit. Despite the failures of these new drugs to eradicate the infection, they had done more—in tempering the fever and even in ridding the blood stream of streptococci, if only briefly—than any of the variegated measures had accomplished against this disease through the years. By doing so, they raised the hope

monary circuit, and (c) cutting off this aortic current which acts to dilate the pulmonary artery and its branches and to drive the organisms through, thereby aiding the lung capillaries to filter out the organisms. Libman<sup>20</sup> believes that recovery is influenced largely by the cutting off of the supply of arterial blood to the organisms on the pulmonic side of the closure and the decreasing of tension within the pulmonary artery.

In the ligated non-infected ductus, these same factors, we should believe, would tend to avoid or abort later infection. Surgical closure also would block the aortic current from roughening further the endothelium of the pulmonary artery and pulmonic end of the ductus, and from causing turbulence in them, both of which favor bacterial implantation. Persisting irregularities already present there, however, might serve as a nidus of infection, as might the ostium or cul-de-sac at the aortic end of the ductus. Gross<sup>20</sup> stresses that ligation often fails to obliterate the ductus completely, and that the remaining tiny opening may permit swirling into the pulmonary artery favorable to implantation; complete division would eliminate this factor. Of 81 successfully-operated-upon non-infected cases reviewed by Shapiro and Keys,<sup>21</sup> two<sup>20, 22</sup> later developed subacute bacterial endarteritis. In one, the ductus had previously re-canalized such an event (believed to have occurred in 14 of the 81 cases) would negate any value in avoiding infection. More extensive and accurate data as to the incidence of infection in the untreated patent ductus, and long observation of the surgically-treated non-infected cases, are needed to judge the worth of the operation as a preventative of bacterial endarteritis.

that the day of successful treatment of subacute bacterial endocarditis might not be far distant

### SUMMARY AND CONCLUSIONS

1 A series of 250 well-substantiated cases of subacute bacterial (streptococcal) endocarditis studied in five Boston hospitals and in private practice from January 1927 to March 1939 has been analyzed for three purposes (a) to evaluate more completely the clinical picture, (b) to establish a baseline of prognosis, especially as a means by which the effects of therapy can be measured, and (c) to determine the results of treatment prior to the intensive use of the newer chemotherapeutic drugs and the anticoagulants. All the patients had cultures positive for nonhemolytic streptococci of the alpha (viridans) or, rarely, the gamma (nonhemolytic) variety. In these clinically definite cases, with two or more positive blood cultures as a rule, the ratio of positive cultures to all cultures taken was 74.4 per cent, being 66.8 per cent from 1927 through 1932 and 78.8 per cent from 1933 through 1938.

2 The male sex was preponderant in the ratio of about 2 to 1 (161 to 89, or 64.4 per cent to 35.6 per cent).

3 The average age of the entire group was 31.8 years, with a range from 2½ to 78. The majority of the cases were in the third and fourth decades, the former predominating with 80 patients. The average age of females (25.7 years) was distinctly less than that of males (35.2 years).

4 The great majority of the 250 cases had rheumatic heart disease (224 or 89.6 per cent—though the rare possibility of a previously unimpaired heart could not be completely excluded in some of those who were not autopsied, in two of 57 autopsied cases, hearts believed clinically to show rheumatic [mitral] disease presented no apparent preëxisting lesions)\*. Mitral valve involvement alone (usually regurgitation) was diagnosed in 96 (42.9 per cent of the rheumatic group). Aortic valve involvement was diagnosed in 130 cases (58.0 per cent of the rheumatic group), divided into two cases of stenosis, 106 of regurgitation, and 22 of stenosis and regurgitation. Of these 106 cases, 74 also had mitral diastolic murmurs, which may or may not have denoted mitral stenosis†—or even prior rheumatic mitral disease, the apical systolic murmur present in most of the group was likewise not necessarily diagnostic of organic mitral disease, and for this reason it is not possible to break down the group into uncomplicated aortic and combined aortic and mitral lesions. Congenital defects were diagnosed in 13 patients or 5.2 per cent of the 250 cases, including five instances of patency of the ductus arteriosus and five cases of ventricular septal defect.

5 The most common predisposing cause of the illness in the cases studied, if we exclude the indefinite condition called gripe—which may

\* These two cases are excluded from the rheumatic group but left in the sub-group diagnosed as mitral valve involvement thus giving 226 (100.0 per cent) for a total of the component sub-groups rather than 224 cases.

† See P. 58, No. 9.

have been the early stage of the disease itself—was some dental procedure, especially extraction. Exact figures are not possible in this series, for often no statement about previous dental treatment was included in the history, but it is estimated that almost one in four cases of subacute bacterial endocarditis gives such a history if inquiry is made. It has been stressed that individuals susceptible to this disease should be particularly attentive to the care of their teeth and should avoid harsh dentistry and extractions not clearly indicated.

6 The incidence of salient clinical findings in this group of 250 cases was as follows: heart murmurs in 99.2 per cent, petechial hemorrhages in 86.5 per cent, palpable spleen in 59.0 per cent, hematuria in 49.0 per cent, clubbed fingers in 46.7 per cent, and chills in 40.5 per cent. It was not the rule to find all these conditions present in the same patient, for example, splenomegaly, clubbing, and petechiae were present together in only 13.1 per cent, and none of these three significant findings in as many as 6.1 per cent.

7 The differential diagnosis of subacute bacterial (streptococcal) endocarditis includes a consideration of many different diseases. Those more commonly considered in the present series of cases were "grippe," rheumatic fever, renal calculus, meningitis, pleurisy, tuberculosis, pneumonia, subarachnoid and cerebral hemorrhage, brain tumor and abscess, central nervous system and latent syphilis, and angina pectoris. Among those less commonly considered, there were acute appendicitis, neuritis, undulant, typhoid, and typhus fevers, perinephric and subphrenic abscess, and portal thrombophlebitis. The commoner manifestations of the disease, namely, fever, local symptoms from embolism to the brain or spleen or other viscera, and renal involvement, were the reason for this wide diversity of suspected diseases. It has been emphasized that fever and malaise in a patient with a heart murmur may mean subacute bacterial endocarditis, and, unless another cause is clearly recognized, it is important to confirm or exclude the diagnosis by repeated blood cultures.

8 Analysis of this series revealed instances of the concurrence of rheumatic fever and subacute bacterial endocarditis. It appears that the latter disease may serve as a factor to activate rheumatic fever in susceptible individuals, and also that bacterial endocarditis may arise during the course of rheumatic infection.

9 Chronic rheumatic mitral stenosis was too often diagnosed in the presence of a mitral diastolic murmur, which in a number of cases that came to autopsy was apparently the result of dilatation of the left ventricle or of vegetations on the mitral valve, only three of 19 cases, 10 with and nine without aortic regurgitation, diagnosed as having mitral stenosis during life, showed such stenosis at autopsy.

10 Of the 250 cases of subacute bacterial (streptococcal) endocarditis studied, 246 were adequately followed up and all died of the disease except one who succumbed to rheumatic myocarditis after a period of one year of freedom from evidence of bacterial endocarditis.

11 The duration of the disease to death averaged 5.9 months, with longer duration for females (7.0 months) than for males (5.3 months). The numerically largest group survived three to four months, the second largest four to five months. The longest survivor lived 19 months. An appreciable number—18—lived more than a year.

12 No therapy was curative. Occasionally there seemed to be a temporary effect on the disease from some of the measures tried, but it must be remembered that the disease itself has a markedly variable course. Therapy included whole blood transfusions in 45 patients, and transfusions from immunized donors in three cases and from a "recovered" patient in one, bacteriophage in eight, autogenous vaccines in nine cases, stock vaccines in two, antistreptococcal serum of various kinds in seven and inoculation with living organisms from the patient's blood in five. Injections intramuscularly of sterile milk and of turpentine were administered in two cases each, and hyperthermia, radiotherapy, and ultraviolet radiation in a few scattered instances. Various chemicals were used, including sodium cacodylate in four, neoarsphenamine in two, metaphen in two, acriflavine in two, gentian violet in three, mercurochrome in three, and in the early days of sulfonamide therapy, Prontosil in five, sulfanilamide in 24, and sulfapyridine in four. Use of this last group of drugs was followed in some cases by reduced fever and negative blood cultures, neither of which persisted.

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NOTES ON THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS ENCOUNTERED IN 88 CASES AT THE MASSACHUSETTS GENERAL HOSPITAL DURING THE SIX YEAR PERIOD 1939 TO 1944 (INCLUSIVE)

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IN this note we shall report the findings in the 88 clearcut cases of subacute bacterial endocarditis which were treated at the Massachusetts General Hospital for the nearly-six years from the beginning of 1939, which terminated the period of 12 years covered in the analysis of Kelson and White<sup>1</sup> presented above and began a period of special chemotherapy (January 1939–November 1944 inclusive). The first seven cases were reported by Kelson and White in 1939.<sup>2</sup> Thirty-eight more of these 88 cases were reported by Leach et al in 1941.<sup>3</sup> Forty-three new cases have been treated since. Our criteria for a clearcut case have been the usual clinical findings backed by three positive blood cultures or confirmation at autopsy. There were two recoveries in the first seven cases reported by Kelson and White in 1939, one of these is still alive and well, the other died later of acute rheumatic heart disease.

Forty-nine (55.8 per cent) of the 88 cases were males. The ages varied from 14 to 70 years with an average age of 31.8 years. All patients had heart murmurs. A diagnosis of chronic rheumatic heart disease was made in 76 cases, and the classification as to valves involved in order of frequency was mitral, mitral and aortic, and aortic alone. Congenital lesions were found in 12 cases with the following frequency: patent ductus arteriosus six times, bicuspid aortic valve alone twice, interventricular septal defect alone twice, bicuspid aortic valve and interventricular septal defect with vegetations on both lesions once, and interventricular septal defect plus rheumatic heart disease with aortic stenosis and insufficiency, vegetations being found at necropsy on both defects, once.

#### BACTERIOLOGY

The diagnosis was established bacteriologically ante mortem in 83 cases (94.3 per cent) and by autopsy in the remaining five. All of the 83 had at least three positive blood cultures, and the majority had more. The alpha

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hemolytic streptococcus was the offending organism in all the 88 cases, except 12, in which the *Staphylococcus albus* was the causative organism in two, the nonhemolytic streptococcus in six, *H influenzae* in two, the non-hemolytic *Streptococcus fecalis* in one, and the beta hemolytic streptococcus in one. In the five cases confirmed by postmortem examination the bacterial findings ante mortem were as follows: two had two positive cultures for alpha hemolytic streptococci and three had consistently negative cultures. One of these had 15 negative cultures, but at necropsy type 13 pneumococci were obtained from the heart's blood. Alpha hemolytic streptococci were found post mortem in the heart's blood in three of the remaining four cases and were grown from the heart valves in the other.

### TREATMENT

All of the patients were given high vitamin high caloric diets, and most of them supplementary iron and vitamin concentrates. Transfusions and other supportive measures were carried out as indicated. Forty-five received sulfonamides alone, 32 received additional therapy as well, two had no treatment other than general measures, and since January 1944 nine have been given penicillin, some with and some without sulfonamides. Six of the patients, treated with sulfonamides only, received grossly inadequate therapy for one reason or another (five patients received one or two days of medication only and the other, four days of treatment terminally). Until the latter part of 1941 sulfonamide therapy was most frequently initiated with sulfapyridine, changing sequentially to sulfathiazole or sulfanilamide, depending on the response of the patient. However, after that time sulfadiazine became the starting drug of choice. Of the 32 who received additional therapy in the form of a single preparation or of combinations, 17 received heparin (11 for five days or less, one for seven days, and five for 10 to 23 days), six intravenous typhoid vaccine, four sodium parantrobenzoate, two neoarsphenamine, and five of the more recent ones, dicoumarin which is now replacing heparin in the therapy of some of our cases. One of the patients who had less than five days of heparin therapy received inadequate sulfonamide therapy as well (three days' treatment terminally). Heparin was given in such a quantity as to keep the clotting time at approximately one hour. Twenty cubic centimeters given in isotonic saline or glucose in 24 hours usually sufficed. Dicoumarin was given in an average dose of from 100 to 200 mg per day in order to maintain a prothrombin time of 40 to 60 seconds. The normal prothrombin time was determined against a control which usually varied from 18 to 22 seconds. Four of the patients after a rather prolonged trial on chemotherapy, were given hyperthermia by means of a fever cabinet, without obvious beneficial effect. This treatment was kindly carried out for us by Dr John Gibson of the Peter Bent Brigham Hospital.

## RESULTS FROM SULFONAMIDE THERAPY

Of the 77 patients who received sulfonamide therapy, including the six who received grossly inadequate amounts, 66 died, five recovered, follow-up information was not obtained on five, and one was still living but was not in good health three and one-half years after leaving the hospital (Case 6). This patient has not been included in the list of recovered cases despite the facts that she had been reasonably well without medication for more than three years and that three blood cultures had been negative, because we have not ourselves been able to see her during the last 1½ years, this very duration of life, namely 3½ years since the original illness, does of course strongly point to recovery from the subacute bacterial endocarditis, a recent report from her doctor states that she is now having a "recurrence of rheumatic fever." Three of the recovered patients have been well for two, three, and five years although one is now convalescing from active rheumatic fever. The other two "cures" were proved at autopsy, one patient dying from an unrelated accident, and the other from acute rheumatic fever. One of the patients who recovered received four days of heparin therapy which was thought not to have altered the course of the disease. Blood cultures became negative and rectal temperatures were reduced to 98.6° to 100° F during sulfonamide therapy before heparin was started on another patient who recovered. One of the remaining 15 patients who received heparin (seven of whom received five days or less of medication) recovered, but none of the other patients who were given additional treatment survived. Thus, five (6.5 per cent) of the 77 patients who received sulfonamides recovered, and one remains unclassified as yet.

Fifty-two of the 77 sulfonamide-treated patients showed a definite partial to complete loss of fever within one to three days after treatment was instituted, the afebrile state lasting from two to 12 days. One patient who received typhoid in addition to sulfonamides had normal temperature consistently between episodes of artificially induced fever. Subsequently, various degrees of fever returned in the patients who died, despite continued medication. The other 24 patients showed little or no response to the drugs. Sulfapyridine appeared to have a greater antipyretic effect than the other sulfonamides.

One of the two patients in whom the *Staphylococcus albus* was the causative organism recovered.

The following are summaries of the cases in which recovery occurred.

## CASE REPORTS

*Case 1* (previously reported<sup>1</sup>) E. S., a 21 year old man, was admitted to the hospital in April 1939 because of fatigue, anorexia, fever, headaches, and chilly sensations of four days' duration. He had had rheumatic fever at the ages of 10, 11, and 13 years. Three blood cultures taken before admission were positive for *Streptococcus viridans*. He appeared poorly nourished and chronically ill. Systolic and diastolic murmurs were present at the aortic and mitral areas. His temperature was

104.6° F rectally. He was given 6 grams of sulfapyridine daily and on the second day his temperature dropped to 101° F rectally. He complained of joint pains and his electrocardiogram showed partial auriculoventricular block. Eight days later heparin was started and was continued for two weeks. During this time the rectal temperature dropped to 99 to 100° F. Sulfapyridine was continued for two more weeks. A few weeks later auricular fibrillation occurred. Slight fever persisted, but it was thought that the subacute bacterial endocarditis was arrested and that he now had active rheumatic fever. Nineteen consecutive blood cultures were negative. He died in congestive failure four months later when postmortem examination revealed evidence of acute and chronic rheumatic heart disease and healed, calcified vegetations of bacterial endocarditis on the mitral valve. Ground fragments of these vegetations showed no growth on culture and microscopic examination of the involved valve and vegetations showed no bacteria.

*Case 2 (reported previously<sup>1</sup>)* A C, a 23 year old woman, was admitted to the hospital in April 1939 because of chilly sensations, fever, malaise and joint pains for five months. She had had rheumatic fever at 10 years of age. A blood culture taken three months before admission was positive for alpha hemolytic streptococci. She appeared undernourished and pale. Systolic murmurs were heard in the aortic and mitral areas and several petechiae were found. Two further blood cultures were positive, so sulfapyridine was started on the seventh hospital day. Blood cultures became negative and rectal temperatures ranged from 98.6° to 100° F. Heparin was started on the seventeenth day and continued through the thirty-fourth day. Sulfapyridine was continued for eight more days. Blood cultures were negative and the patient remained in excellent health without medication until December, 1943 when she had a "cold" and following that began to lose weight and noticed that she became more easily fatigued. In September, 1944 she had to be readmitted with a diagnosis of active rheumatic fever. Eight days before admission she had nosebleeds and hot flashes with a "cold." Blood cultures during hospitalization were negative and there was no evidence of subacute bacterial endocarditis. She was dismissed on October 20, 1944 to remain in bed at home and when last seen, December 1, she was convalescing satisfactorily from her acute rheumatic infection.

*Case 3 (previously reported<sup>2</sup>)* W N, a 21 year old male with a patent ductus arteriosus, who had been told five months previously that he had a streptococcal infection in his blood, was admitted in June 1940. He was thin and appeared chronically ill. Four out of five blood cultures were positive for alpha hemolytic streptococci. The fever responded immediately to sulfapyridine, rose to 103° F. 10 days later, and returned to normal by the fifteenth day. On the seventeenth day heparin was started and continued for four days when the temperature increased to 102.5° F and a macular rash appeared. All medication was then stopped. The rash recurred every time sulfapyridine was resumed and so sulfathiazole was tried. After seven days of this treatment, an erythema nodosum-like rash appeared which subsided along with the fever three days after the dose was reduced from six to three grams daily. This dose was continued for six more months. In March 1941 the patent ductus was ligated by Dr. Robert Gross who could palpate no vegetations of subacute bacterial endocarditis. While in excellent health the patient was killed in an automobile accident in July 1941. Autopsy revealed a few small, slightly raised areas in the pulmonary artery close to the mouth of the ductus arteriosus and on the pulmonary aspects of the pulmonary valve cusps without evidence of inflammation or vegetations.

*Case 4* M R, a 33 year old female who had chronic rheumatic aortic and mitral stenosis and insufficiency, entered the hospital in November 1941, with a history of having had a sore throat for three days and chills and fever for three months. Her temperature on admission was 102.8° F, and the first three blood cultures were positive.

for alpha hemolytic streptococci. There was an immediate and permanent disappearance of the fever with sulfadiazine, and no positive blood cultures were obtained after treatment was instituted. She was discharged improved on December 18, 1941 on a four gram daily dose of sulfadiazine which was continued until May 20, 1942. Since then to date she has remained well without medication.

**Case 5** G B, an 18 year old girl with chronic rheumatic aortic and mitral stenosis and insufficiency, was admitted on January 10, 1942 with a history of having had numerous red spots on her legs seven months previously. After that time she had daily fever, sensations of pressure in the precordium, fatigue, anorexia, and weight loss. The highest known temperature was 102° F. On physical examination the lower pole of the spleen was found to be four fingers below the left costal margin. Five of 10 blood cultures were positive for *Staphylococcus albus*. There was an immediate partial response of the fever during the first four days of sulfathiazole therapy, followed by complete and permanent reduction of the fever and persistently negative blood cultures. She was perfectly well when last seen in the Cardiac Clinic on June 14, 1944. The spleen was no longer palpable.

**Case 6** E A, a 23 year old woman, was admitted to the hospital in February 1941 because of pain in her left upper abdominal quadrant, sore finger tips, and red painful areas on her legs during the preceding six weeks. Physical examination revealed a pale, well developed woman. The heart was slightly enlarged and systolic and diastolic murmurs were heard in the mitral area. Several petechiae were seen. During the hospital stay embolic phenomena were observed and three blood cultures were positive for alpha hemolytic streptococci. There was almost a complete response of her fever to sulfapyridine for five days, but by the eighth day her temperature was 104° F and she had developed generalized lymphadenopathy and an erythematous rash. Her temperature returned to normal the next day after stopping the drug. Marked systemic reactions occurred after resuming sulfonamides on two later occasions. During the first seven weeks after her discharge from the hospital on April 23, 1941, without medication, she noticed painful finger tips on two occasions. Blood cultures remained negative, however. A molar tooth was extracted on September 23, 1941 at which time she took sulfadiazine for four days without deleterious effect. A blood culture was negative at this time. She was not seen again until May 1943, when physical examination revealed evidence of infection (fever, leukocytosis, and a rapid sedimentation rate), anemia, cardiac murmurs as before, and an enlarged spleen. One blood culture was negative. She stated that she had not had fever or petechiae in the interim of one and one-half years, but we could not be certain that this statement was correct since she did not think she had fever when we examined her.

She was not gotten in touch with again until December 11, 1944 when her local physician stated that she had been well except for occasional episodes of acute rheumatic fever. He saw her on December 11 because of joint pains and swelling which began on December 10 and he thought that she again had rheumatic fever.

During the same period, four patients who probably had subacute bacterial endocarditis but did not fulfill our criteria for clearcut cases were treated in the hospital. All showed evidence of the infection superimposed on chronic rheumatic valvular involvement or congenital heart disease. Two had two positive blood cultures each for alpha hemolytic streptococci and the other two had one positive culture each. One patient received inadequate therapy and two no treatment. Three of the patients died and one recovered.

The following is a history of the patient who recovered.

*W. E.*, a 38 year old male with chronic rheumatic aortic and mitral valve disease, was admitted in April 1941 with a history of having had influenza five months previously, trouble with his joints for four months, malaise, and fever. While in the hospital he had definite evidence of emboli and one of three blood cultures was positive for alpha hemolytic streptococci. There was an immediate favorable response to sulfathiazole which he took for 27 days, since when he has been perfectly well without medication.

### RESULTS FROM PENICILLIN THERAPY

Since January 1944 when penicillin became available for use in small quantities, nine cases of subacute bacterial endocarditis have been treated at the Massachusetts General Hospital and Baker Memorial Hospital with penicillin, sometimes in combination with the sulfonamides, and the results have so far been encouraging although the follow-up period has been brief.\*

Eight of the nine cases had rheumatic heart disease, the only clinically demonstrable lesion in five was mitral regurgitation, one had mitral stenosis and regurgitation with auricular fibrillation, one had aortic stenosis and probable mitral stenosis, and the eighth had both aortic and mitral regurgitation. There was one case of congenital heart disease with an interventricular septal defect. The group consisted of six females and three males whose ages ranged from 17 to 70 years. The alpha-hemolytic streptococcus was found in six cases, the non-hemolytic streptococcus in two cases, and the beta-hemolytic streptococcus in one case. The dosage of penicillin varied from 100,000 to 288,000 units daily for two to four weeks, the average case being given 200,000 units daily for three weeks. Three patients received sulfonamide before penicillin was given, one received penicillin with sulfonamides, one received penicillin alone during hospital treatment but was sent home on sulfadiazine, and four received penicillin alone.

To date (December 8, 1944) two patients have died, the first of cerebral embolism which occurred on the fourteenth day of treatment so that although there was a fall in temperature after penicillin was started, a normal level was never reached, and there was no way of evaluating therapy. The second died eight months after the completion of her course of penicillin, apparently from active rheumatic fever with cardiac failure complicated by

\* Since this paper went to press four patients, three with rheumatic heart disease and one with congenital heart disease, have been admitted for treatment of subacute bacterial endocarditis, and three of these have to date (December 27) received penicillin. The first patient, a 27 year old man, received 2,280,000 units at another hospital, but after admission here on October 19, he had one culture positive for the alpha-hemolytic streptococcus and a splenic infarction so that a second course of therapy was begun on November 25. After three weeks of treatment he was sent home in excellent condition. The second patient, a 54 year old woman, continued to have low grade fever after the urinary infection for which she was admitted had subsided. Blood cultures showed *Staphylococcus albus*, and penicillin was started on December 1, to date (December 27) after three weeks' treatment she has become afebrile and feels much better. The third patient, a 56 year old man whose blood cultures were positive for nonhemolytic streptococci, has become afebrile after three weeks' treatment. The fourth patient, an 18 year old boy with congenital heart disease, was given six weeks' intensive treatment with penicillin in another hospital but since admission here, blood cultures have shown alpha-hemolytic streptococci, and he has had slight temperature elevation uncontrolled by sulfadiazine.

renal disease and possibly nutritional deficiency. Blood cultures were repeatedly negative, and she was bacteriologically "cured." Postmortem examination was not obtainable.

The remaining seven patients had a marked fall in temperature from one to four days after therapy was begun, and the temperature became normal within 9 to 27 days. Four of these seven cases are now apparently well, three being clinical and bacteriological "cures" approximately seven weeks, five months, and eight months after completion of one course of therapy, the fourth had a recurrence of the infection but is well two months after a second course of penicillin. This fourth patient was readmitted six weeks after discharge because of low grade fever and chest pain, and a blood culture taken on the day of admission showed nonhemolytic streptococci again, she was given a second three weeks' course of penicillin, and when she returned for examination on November 24, 1944 she was free of any evidence of infection. Of these four apparent "cures" one received penicillin alone, one had sulfonamides before penicillin was started, one had sulfadiazine during the last ten days of penicillin therapy, and after its completion, and the fourth case mentioned above who had a recurrence of the infection received sulfadiazine in the interim between the two courses of penicillin.

The fifth case of the seven survivors, a 58 year old woman, developed congestive failure during treatment and is now invalided by increasing dyspnea and edema for which she receives frequent injections of mercurpurin, she has no clinical signs of subacute bacterial endocarditis, however, seven months after completion of therapy. There has been a question of recurrence in the remaining two cases, one of whom has returned for further therapy. This patient was readmitted six days after discharge with a chief complaint of upper abdominal pain, nausea, and vomiting. He had low grade fever and mild congestive failure but blood cultures were negative. There was in his case a question of the recurrence of rheumatic fever, but he was also given a second course of penicillin. His status was still uncertain three weeks after the completion of this treatment as he had just begun to have evening elevation of mouth temperature to 99.2 and 99.8 degrees accompanied by pain in his knee, calf, and instep. The last case of the seven survivors was apparently well for one month after the completion of his course of penicillin on November 4, 1944, but reported on December 9 that he had been having fever in the evenings of 99.5 to 100.8 degrees (by mouth) since December 6. He did not feel as well as usual although there was no joint pain, cough, or dyspnea.

*Case 1* I. J. D. is a 23 year old white female who was admitted to the hospital December 20, 1943. She developed mitral stenosis and regurgitation after acute rheumatic fever at the age of 15, but had no symptoms until the age of 18 when she suffered from dyspnea and auricular fibrillation. She was maintained satisfactorily after that on digitalis and quinidine, she did secretarial work for a while, later married, and went through an apparently normal pregnancy. Her present illness began one month before her admission with an attack of the "flu" after which fever and

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*Case 1* I J D is a 23 year old white female who was admitted to the hospital December 20, 1943. She developed mitral stenosis and regurgitation after acute rheumatic fever at the age of 15, but had no symptoms until the age of 18 when she suffered from dyspnea and auricular fibrillation. She was maintained satisfactorily after that on digitalis and quinidine, she did secretarial work for a while, later married, and went through an apparently normal pregnancy. Her present illness began one month before her admission with an attack of the "flu" after which fever and



cough persisted. Blood cultures were found positive for the alpha hemolytic streptococcus, and she was given sulfadiazine for two and a half days and then sulfapyridine (6 gm and then 4 gm daily) for twelve and a half days. Her temperature fell to normal the third day after this medication was begun and remained normal for three days, it rose immediately after that and continued high although she remained on sulfapyridine. Penicillin therapy was begun on January 11, 1944, eight days after sulfonamide was stopped, 200,000 units being given either intravenously or intramuscularly every day for two weeks. There was an almost immediate fall of the temperature to a lower although not to a normal level for two days. During the following seven days the temperature rose again and stayed between 101° and 104°, after that it gradually fell to a lower level so that for the last two weeks of her hospital stay it ranged from 98.6° to 100.5° F by rectum. The prognosis at the time of her dismissal on February 9, 1944 was unfavorable.

After her return home she failed to begin her temperature record until March 4, but it was normal then and remained normal or subnormal until the first part of April. Her blood cultures which became negative by January 31 remained negative and have continued to show no growth through September, 1944. She was symptom free after dismissal until she developed slight congestive failure during the early part of April, the congestive failure was followed by thrombophlebitis of the left leg, pulmonary infarction, and iliac phlebitis for which ligation of the inferior vena cava was done on April 13. Recovery from this was uneventful, the temperature remained normal and she continued symptom free except for some increasing congestive failure and another mild episode of thrombophlebitis on the right. On her last visit during August 1944 she was found to have marked edema of the face, sacrum, and both lower extremities. The exact cause of the edema was undetermined, although she responded to routine therapy in the hospital, several factors seemed to be responsible—cardiac failure, hypoproteinemia and renal failure, and she also probably had acute rheumatic fever. However, blood cultures which were taken repeatedly were negative. She was convalescing in the hospital and her condition was apparently satisfactory when she had cerebral embolism with left hemiparesis on September 24 and died on September 30.

*Case 2* K. M. is a 27 year old white female who was admitted to the Baker Memorial January 15, 1944 with a chief complaint of epistaxis which had occurred daily for a week and which had lasted for nine or ten hours preceding admission. Her past history revealed a definite episode of rheumatic fever at the age of 11 after which she was told that she had a heart murmur. Her present illness began in November, 1943 during the sixth month of her second pregnancy with slight nonproductive cough, chilly sensations, malaise, anorexia, and fever so that she thought she had "grippe". In December the same symptoms recurred, and she had a temperature of 101° F. On January 5, 10 days before admission she had acute back pain which forced her to bed, later in the hospital this was considered due to acute sciatica or possible ruptured intervertebral disc. From November 1943 until January 15, 1944 she suffered from malaise, night sweats, and weakness, and thinks she probably had some low-grade fever although she continued to do her housework.

On January 21 she was delivered of a normal female infant which did well. After delivery her temperature was septic in type and rose to as high as 104.5° F. Sulfathiazole was given for eight days from January 30 through February 6 because of the possibility of pyelonephritis. Several blood cultures then became positive for nonhemolytic streptococci, and she showed petechiae. On February 21 she was transferred to the Massachusetts General Hospital where physical examination showed a heart of normal size with a short, harsh systolic murmur at the mitral area, a palpable spleen, and embolic phenomena. On February 19, sulfadiazine was started six grams being given daily until February 29 without any apparent effect on the temperature which ranged from 100° to 104° F. Penicillin therapy was begun on

March 8, 200,000 units being given daily for 21 days by continuous intravenous drip. Her temperature dropped on the second day of treatment to a lower level and stayed between 100° and 101° F with an occasional rise to 102° F until March 30, then it fell to 99 and 100° F by rectum and stayed within a normal range until April 12. On April 12 she had soreness of one wrist and a temperature elevation to 101° F which responded to the administration of salicylates. By April 22 her temperature was again normal and it remained normal until her dismissal on May 13, 1944. Since that time she has been followed in the Cardiac Laboratory. Blood cultures which became negative by March 11 have remained negative through October 1944, and she has remained symptom free through October 1944 and gradually increasing her activity. She was apparently well when last seen on October 31, eight months after completion of the penicillin therapy.

*Case 3* W M is a 38 year old white female who was admitted to the Massachusetts General Hospital on February 14, 1944, with the chief complaint of marked fatigability and night sweats which were noticed for the first time in October 1943 when she also had some palpitation and vague pains in her knees and shoulders. For ten days before admission she had chills every other night and questionable embolic phenomena appeared on one finger and on the internal malleolus. A diagnosis of rheumatic heart disease with aortic and mitral regurgitation had been made on a previous hospital admission although no history of rheumatic fever was elicited. After blood cultures became positive for alpha-hemolytic streptococci, intravenous penicillin therapy was begun on March 29, 200,000 units being given every twenty-four hours. There was an immediate fall in temperature to 100 degrees but a few days later there were elevations to 101 and 102 degrees. On April 11 she had a severe chill after penicillin was started, became comatose, and developed a left hemiplegia. Her temperature rose to 104 degrees and auricular fibrillation appeared. From that time her course was gradually downward until her death on April 19, 1944.

*Case 4* E J is a 58 year old white female who was admitted to the Baker Memorial on April 11, 1944 with a history of pneumonia six weeks before. She was able to be up after the first three weeks of the illness but continued to have anorexia, weakness, and fatigue. On admission she was slightly disoriented, had high fever, a rapid heart rate with a loud systolic murmur at the apex, and numerous petechiae over her body, several blood cultures were positive for the alpha hemolytic streptococcus. Later she had emboli to her kidneys with hematuria and became comatose. She was given a total of 2,800,000 units of penicillin, approximately 100,000 units daily from April 20 through May 2. The temperature which had been fluctuating between 100° and 104° F dropped to a slightly lower level by April 24, the fourth day of therapy, then fluctuated above normal until May 4 when it became normal. It remained normal until dismissal on June 3 except for slight rises on May 18 and June 1. Since dismissal she has been invalided by increasing congestive failure for which she has received digitalis in the hospital and at home since and has to be given mercupurin at five day intervals to relieve dyspnea, and edema. However, her family physician reported on November 21, 1944, that she had had no fever and no clinical manifestations of subacute bacterial endocarditis. No recent blood cultures have been obtained.

*Case 5* A C is a 17 year old white female who was admitted to the Baker Memorial on June 2, 1944 because of slight left hemiparesis and fever which had a rather sudden onset two and one half weeks before admission. She had rheumatic fever at the age of 12 and following that developed aortic stenosis and possibly slight mitral stenosis. After cultures became positive for nonhemolytic streptococci penicillin therapy was begun on June 6 a total of 6,600,000 units being given by continuous intravenous drip, at first 100,000 units were given daily and later 300,000 units a day until July 7. Six grams of sulfadiazine were given daily with the penicillin from

June 1 to June 7, and one gram was given on June 8. Her temperature became normal on June 9 and 10 and remained within normal limits until June 16 when it rose to 100° F. On June 17 and 18 it was a little higher than normal and on June 19 it rose to 102° F and fluctuated rather markedly from then until it returned to normal on July 3. On June 23 there was a temperature rise which was probably the result of a delayed transfusion reaction. On June 27 there was a rise to 103° F which was probably due to a splenic infarction on June 26. From July 3 until July 23, rectal temperatures reached 100° F daily but were usually lower than that and never higher. She was discharged on July 23 symptom free with negative blood cultures. There has been no fever since (to date, December 8, 1944).

*Case 6* S H is a 17 year old white female with a known interventricular septal defect who was admitted on June 19, 1944 to the Baker Memorial with a chief complaint of fever. Her present illness began in March with a "cold" followed by pleurisy, cough, and fever. She was in bed for 10 days but then returned to school and was apparently well for about two weeks. However, in April she began having fever ranging from 100 to 101° F which was highest in the evening and was accompanied by drenching sweats. In the hospital, cultures showed alpha hemolytic streptococci, and intravenous penicillin therapy was begun, 25,000 units being given on June 16, 100,000 units daily from June 17 through July 6, and 92,000 units on July 7. Her temperature became normal by June 18, and it remained at 99° F, or below until June 24. On June 25 and June 26 it was a little above 99° F by rectum, and on June 27 it went to 100° F. After that, except for one rise slightly above 99 on July 11, it was normal until discharge. A culture taken on July 5 was negative and she became symptom-free. She was sent home on sulfadiazine grams 1½ daily. She did well for five weeks after dismissal but had to be readmitted on September 5 because of low grade fever which had been present for six nights. Two days before admission she had had pain in her right chest, made worse by coughing. A blood culture on the day of admission showed nonhemolytic streptococci and she was given another three weeks' course of penicillin. Since that time she has been symptom-free and afebrile. She returned for examination on November 24, at that time, two months after completion of her second course, no clinical evidence of infection was present, and blood cultures were negative.

*Case 7* S A H is a 70 year old white male who was admitted to the Massachusetts General Hospital on September 11, 1944 because he had been having chills and night sweats for the previous two to four weeks. He had not been feeling well since May although he had no specific complaints. His past history revealed a questionable episode of rheumatic fever at the age of 14 and a story of angina pectoris for the last five years. On physical examination there was a grade 2 to 3 mitral systolic murmur heard widely over the precordium but neither embolic phenomena nor splenomegaly were present. Three blood cultures showed the alpha-hemolytic streptococcus, and he was given 48,000 units of penicillin intramuscularly on September 21, then 192,000 units daily from September 22 through October 12, and finally 72,000 units on October 13th. His temperature fell to 99 degrees by rectum on September 21 and ranged between 98 and 100 degrees until the day after therapy was discontinued, when it rose again to slightly over 100 degrees and fluctuated between 99.5 and 100 until October 18 when it became normal. He was discharged on October 20, 1944, and felt quite well for three days. On the fourth day he began to have severe upper abdominal pains, anorexia, nausea and vomiting. He was therefore, readmitted on October 26 and was found to be in very mild congestive failure. Blood cultures were repeatedly negative but his temperature ranged from below 98 up to 100 degrees by rectum. He was digitalized, and another three weeks' course of penicillin was begun on October 28. On November 8, after ten afebrile days his temperature rose to 101 and 102 degrees and remained high until

November 12 After that until his dismissal on November 18, it was normal Since that time he has been in a nursing home He was fever-free there and asymptomatic until December 6 when he began to complain of severe burning sensations and cramping pains in his knee, thigh, and instep, and had a slight elevation of temperature to 99.2 and 99.8 degrees His present status to date (December 8) is uncertain although it is thought that his recent illness has been due to active rheumatic fever, there being no evidence of a recurrence of the subacute bacterial endocarditis

*Case 8* J. L. is a 68 year old white male who was admitted to the Massachusetts General Hospital on September 13, 1944, with chief complaints of anorexia and constipation He had stopped work four months before because of "dry heaves" and weakness, and after going to bed at home, developed constipation with occasional diarrhea His past history was noncontributory He denied having chills or fever but in the hospital his rectal temperature ranged from 99 to 102 degrees with an occasional rise to 103 On physical examination he appeared anemic and chronically ill but showed no positive findings otherwise except for a short, grade 2, systolic murmur at the mitral area Several blood cultures were positive for alpha-hemolytic streptococcus, and penicillin therapy was started on September 26 and continued for 23 days, approximately 192,000 units being given daily through October 17 His course was uneventful after the first day of therapy, and his temperature did not go above 99 degrees by mouth or 100 degrees by rectum except on two occasions Blood cultures taken on the second day of treatment were negative, and six others taken at intervals since then, the last on November 8, have also shown no growth He was discharged on October 23 but has been seen since then on November 8 and December 6 He now appears well, is afebrile, and symptom-free

*Case 9* J. F. is a 33 year old white male who became ill with fever five weeks before admission to the Baker Memorial Hospital on October 5, 1944 He was known to have had a heart murmur at the age of five years and gave a rather questionable history of rheumatic fever in childhood On the second day of his illness he was given sulfadiazine, and his fever began to subside However, when the drug was discontinued five days later, his temperature rose to 103 degrees It again subsided with sulfadiazine therapy, and although the drug was stopped it did not go above 102 degrees again but ranged usually between 100 and 101.5 degrees by mouth A blood culture taken one week after the drug was discontinued was negative On physical examination he showed a slightly enlarged heart with a grade 2 mitral systolic murmur and slight clubbing of his fingers Four flasks of blood grew beta-hemolytic streptococci, and penicillin was started, 288,000 units being administered intramuscularly from October 15 through November 4, 1944 Before treatment was begun his mouth temperature ranged for the most part between 100 and 102 degrees After the third day of treatment it did not go above 99 degrees, and after October 29 did not go above 98.6 degrees A blood culture taken on October 25 was negative, and the patient was well for one month following the completion of penicillin therapy On December 6 he began having low grade fever of 99.5 to 100.8 degrees (mouth temperatures) during the evenings, and when last seen on December 12 said that he felt under par He had no joint pains, upper respiratory infection, cough or dyspnea The physical findings were unchanged, his spleen was not palpable, and there were no petechiae It was found that he had a recurrence of the infection and therefore he is receiving penicillin again

### DISCUSSION

We have herewith briefly analyzed the series of 88 clearcut and four probable cases of subacute bacterial endocarditis treated at the Massachusetts

General Hospital from January 1939 to September 1944 inclusive, including the series of seven cases treated with sulfapyridine and heparin by Kelson and White in 1939, for comparison with the series of 250 cases studied in the Boston Hospitals from 1927 to 1939 and reported in the preceding paper by Kelson and White. Five (6.5 per cent) of 77 sulfonamide treated patients who were followed up recovered, and if two other patients who had valvular lesions, fever, embolic phenomena, and at least one positive culture are included, six (7.8 per cent) of 79 recovered. One patient who had been reasonably well without medication for over three years was not included among the list of cures to date because we could not be certain that she ever was cured. Recently she showed evidence of infection (fever, leukocytosis, and an elevated sedimentation rate) despite negative blood cultures. Four of the nine patients who were given penicillin are symptom-free and afebrile, seven weeks, two months, five months and eight months respectively after completion of therapy. One patient was free of infection for seven months after completion of treatment; she had many complications including iliac thrombosis and during the latter part of August severe congestive failure with probable active rheumatic fever. During convalescence from this episode she developed cerebral embolism on September 24 and died on September 30. One case died during treatment, and the other three are still ill, one with congestive heart failure, one with rheumatic fever, and one with recurrent bacterial endocarditis.

The opinion that the milder the infection and the earlier the treatment is instituted, the better the prognosis, is only partially confirmed. Most of the patients who did recover gave histories of several months' duration and showed definite evidence of the disease, whereas other patients with shorter histories of infection and milder symptoms failed to recover. It is possible that when certain bacteria are the causative organisms, the prognosis is better than when the *Streptococcus viridans* is the offending agent. One of our two patients who had positive cultures for *Staphylococcus albus* recovered. The transient antipyretic effect of sulfonamides, especially sulfapyridine, was noted. Fifty-two (68.8 per cent of the 77 sulfonamide treated cases) showed a definite partial to complete loss of fever within one to three days after treatment was instituted, the response lasting from two to 12 days. Sulfapyridine appeared to have a greater antipyretic effect than other sulfonamides.

Seventeen of the total series of 88 cases received heparin in the course of treatment; 11 for five days or less, one for seven days, and five for 10 to 23 days. Three of the five recovered cases had received heparin and two others had not. The unproved case of subacute bacterial endocarditis that recovered had received no heparin. Five of the total series received dicoumarin instead of heparin in addition to the sulfonamides. None of these cases did particularly well during therapy, three died in the hospital, and we have been unable to obtain information about the other two.

Four of the nine cases receiving massive doses of penicillin have remained

clear of evidence of bacterial endocarditis since treatment was stopped from two to eight months ago, but this is too short a time to draw any very definite conclusions, at least a year is needed for adequate follow-up but the results to date are more encouraging than from any other type of treatment. One case died of cerebral embolism during treatment and another from active rheumatic fever and congestive failure following cerebral embolism. The other three cases remain ill, apparently with congestive failure, rheumatic fever, and bacterial endocarditis respectively.

### SUMMARY

1 An analysis has been presented of a series of 88 clearcut and four probable cases of subacute bacterial endocarditis treated at the Massachusetts General Hospital from January 1939 to September 1944 inclusive.

2 Five (6.5 per cent) of 77 sulfonamide treated patients who were followed up recovered and quite possibly a sixth case (case 6), and if two other patients who had valvular lesions, fever, embolic phenomena, and at least one positive culture are included, six (7.8 per cent) or seven (8.9 per cent) of 79 recovered.

3 The opinion that the milder the infection and the earlier the treatment is instituted, the better the prognosis, is only partially confirmed.

4 The transient antipyretic effect of sulfonamides, especially sulfapyridine, was noted. Fifty-two (68.8 per cent) of the 77 sulfonamide treated cases showed a definite partial to complete loss of fever within one to three days after treatment was instituted, the response lasting from two to 12 days. Sulfapyridine appeared to have a greater antipyretic effect than other sulfonamides.

5 Seventeen cases of the sulfonamide series received heparin in the course of treatment, 11 for five days or less, one for seven days, and five for 10 to 23 days. Three of the five recovered cases had received heparin and the other two had not. Five more recent cases were given dicoumarin without effect.

6 Since January 1944 nine cases of subacute bacterial endocarditis have been treated with large doses of penicillin. The results to date are as follows:

a Two of the nine cases have died, one of cerebral embolism during the course of treatment and the second of rheumatic fever eight months after the completion of therapy, apparently bacteriologically "cured."

b One case seems clinically free from infection but has severe congestive failure.

c One case who had to return for a second course of therapy has now been having low grade fever for two days so that his present status is uncertain. He may have active rheumatic fever.

d One case was well for one month after the completion of therapy but

returned on December 12 because of low grade evening rise of temperature. He showed a recurrence of subacute bacterial endocarditis, but at present (December 29) is again controlled by penicillin and sulfadiazine in combination.

*e* Four cases are apparently well. Three are clinical and bacteriological "cures" seven weeks, five months, and eight months after the completion of therapy, and the fourth is well two months after a second three weeks' course of penicillin given for recurrence of the infection.

*f* Thus six of these nine cases (67%) have shown a definite control (perhaps a cure) of their subacute bacterial endocarditis by "massive" doses of penicillin, two of these six cases, however, developed other serious complications, namely rheumatic fever and congestive heart failure respectively.

*g* A follow-up note of this series will be presented at the end of another year, at which time a more accurate appraisal can be given.

7 Important complications of subacute bacterial endocarditis that tend to be too little emphasized are cerebral embolism, acute rheumatic infection, and congestive failure, alone or in combination. At the present time these three conditions, as noted above, are on occasion serious drawbacks to complete recovery, even in the very cases that seem to be reacting so well to the massive penicillin therapy.

The authors acknowledge with thanks the kindness of Massachusetts General Hospital staff members in permitting the inclusion of the records of several of their private patients in the series of cases herewith reported, and of Dr Chester Keefer in supplying the penicillin in more ample dosage for the cases treated with that drug during the early months of 1944.

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# OBSERVATIONS ON THE TREATMENT OF SUB-ACUTE BACTERIAL (STREPTOCOCCAL) ENDOCARDITIS SINCE 1939 \*

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ANALYSIS of 250 well-authenticated cases of subacute bacterial (streptococcal) endocarditis studied during the years from 1927 to 1939 disclosed the ineffectiveness of all methods of therapy prior to the introduction of the sulfonamide drugs.<sup>1</sup> Sulfanilamide and particularly sulfapyridine appeared favorably to influence the course of the infection, in some instances, reduced fever and negative blood cultures temporarily followed the use of these drugs. Subsequent experience in the treatment of this disease has made clearer the effects of sulfanilamide and its derivatives, which are shown in the following summary. Some of the cases treated with sulfanilamide and sulfapyridine were collected from other clinics by Dr. Paul D. White and the author, the others were treated personally. Only instances in which the drugs were given prolonged and intensive trials have been included.

*Sulfanilamide* Used in 52 patients, the drug occasionally reduced the fever and rendered blood cultures negative, but no lasting benefit resulted in any instance.

*Sulfapyridine* In 197 patients, this drug lowered the temperature in a majority, with blood cultures frequently becoming negative. Except in four instances, however, these effects were transitory, lasting from a few days to two months. The four cases apparently cured were caused by the gonococcus together with a non-hemolytic anaerobic streptococcus in one instance,<sup>2</sup> and by the *Streptococcus viridans* in the others.<sup>3,4</sup>

*Sulfathiazole* In 23 cases, this drug gave temporary improvement in four.

*Sulfadiazine* In 12 cases, this drug gave temporary benefit in two.

On the basis of the finding by White and Parker<sup>5,6</sup> that the sulfonamide drugs have greater antibacterial activity at higher temperatures, Solomon proposed the use of sulfapyridine or sulfanilamide in combination with intravenous typho-paratyphoid vaccine.<sup>7</sup> We have followed this method, using sulfapyridine—in some instances supplemented with related drugs—together with injections of the vaccine, intensively in 12 patients, with transitory benefit in three.

As a result of its effectiveness in bacteriostatic tests in tissue-culture,<sup>8</sup> Osgood advocated the use of neoarsphenamine, alone or in conjunction with sulfathiazole.<sup>9</sup> We have administered this treatment to eight patients without benefit.

In addition to these measures, we have tried a variety of others, all

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without success sulfamethylthiazole, acetyl sulfanilamide (Sulamyd), sulfhydrothiazole, two or more sulfonamide drugs in combination, hyperthermia combined with the sulfonamides, precordial diathermy with the sulfonamides, typhoid vaccine with heparin and the sulfonamides, autotransfusion of blood irradiated with ultraviolet light, induced anaphylactoid shock, and in two cases intravenous injections of tyrothricin (gramicidin plus tyrocidine)

### APPARENT RECOVERIES SINCE 1939

To supplement this experience of our own and further to evaluate the status of treatment, we have analyzed and tabulated the apparent recoveries from subacute bacterial (streptococcal) endocarditis as reported from 1939 to the present time (August 1944) (table 1) \*. A critical search of the literature disclosed a number of other cases which could not be included as authentic instances of recovery from this disease. Some had had no positive blood cultures. Others lacked the clinical picture of bacterial endocarditis—presenting at times the findings of rheumatic fever or even of a blood dyscrasia, and the diagnoses were based primarily on one or two positive cultures, which, clearly, were incidental bacteremias. Still other cases reported as cured were lost from observation after brief periods †. Progress in the treatment of this disease requires accurate diagnosis and careful follow-up of patients. No attempt has been made to evaluate the various methods of treatment on the basis of the percentage of apparent recoveries in pooled statistics, successes are apt to be reported and failures not, though the failures of new or unusual methods are more likely to appear in print than those of simpler, virtually routine measures like the use of the sulfonamides alone. More important, among such groups of cases are a large number allegedly treated by a previously described technic, but in fact given widely different therapy. This has been strikingly true of many cases reported as using the sulfapyridine-heparin method, but in effect employing heparin alone, often because that drug was administered well after sulfapyridine had been begun and had spent its action. Such cases, and those treated with insufficient care or persistency, by no means constitute a valid test of any advocated method ‡.

\* Unreported cases—some mentioned in the literature as having been treated by other workers, but not described—undoubtedly have been treated successfully, but are difficult to collect and analyze and impossible for the reader to study and verify, and so are omitted.

† Some patients were again showing evidence of infection at the time of premature publication of their "recovery," or did so shortly afterward.

‡ Illustrative of such cases from which statistics are made and methods of therapy judged is a series of four recently reported<sup>20</sup> as examples (and failures) of combined heparin-sulfonamide treatment. In case 1, nausea followed the use of sulfapyridine, which was discontinued, apparently on the same day, heparin begun two days later, was given for seven days without accompanying chemotherapy. In case 2, sulfanilamide and sulfathiazole failed to influence the infection, but nevertheless heparin was continued with these drugs for six weeks. In case 3, sulfapyridine was omitted because of nausea and vomiting, and heparin given for nine days along with sulfathiazole, which was ineffective. In case 4, sulfapyridine was given for seven days by rectum, with low (17 mg. per cent) blood concentration, and 11 mg. after a lapse of five days, followed by 25 mg. (with blood cultures remaining positive) for nine days, heparin was given only during these four days and a total of 60 days. During heparin treatment, patient 2 also received arsenical therapy as did patient 3 in the months following discontinuance of heparin.

TABLE I  
Apparent Recoveries from Subacute Bacterial (Streptococcal) Endocarditis Reported since 1939

Author	Num-ber of Cases	Underlying Heart Disease	Specific Treatment	Reference
WELCH, F E, and SOUTHWOOD, A R	1	Rheumatic, mitral	None	Med Jr Australia, 1939, i, 392
LONG, P H, and BLISS, E A <sup>(a)</sup>	4 1	Congenital Rheumatic, mitral	Sulfanilamide	Clinical use of sulfanilamide and sulfa- pyridine and allied compounds, 1939, Macmillan, New York, p 179
MAJOR, R H, and LUGER, L H	1	Rheumatic, mitral	Neoprontosil and sulfapyridine	Jr Kansas Med Soc, 1939, xl, 324
SPINK, W W., and CRAGO, L H	1	Patent ductus arteriosus	Sulfanilamide	Arch Int Med, 1939, lxiv, 228
BARTON, R L, and STRINGER, D	1	Congenital?	Sulfanilamide	Jr Iowa State Med Soc, 1939, xxix, 402
ORGAIN, E S, and POSTON, M A <sup>(a)</sup>	1	Apparently none Implan- tation on pulmonic valve	Sulfapyridine	New England Jr Med, 1939, ccxxi, 167
KILSON, S R, and WHITE, P D	1	Rheumatic, mitral and aortic	Sulfapyridine and heparin	Jr Am Med Assoc, 1939, cxviii, 1700
MAJOR, R H	1	Rheumatic, mitral	Sulfapyridine	Am Jr Med Sci, 1940, cxci, 759
HIVMAN, J	1	Rheumatic, mitral	Sulfanilamide	Jr Am Med Assoc, 1940, cxiv, 2373
FOURQRT, A S W, and VESSIL, H	1	Patent ductus arteriosus	Surgical closure	Jr Am Med Assoc, 1940, cxv, 1270

<sup>(a)</sup> These five cases were among the first group of "more than 60" observed by these authors. Two more apparent recoveries occurred when the group had enlarged to 117. The additional cases have not been reported.

<sup>(b)</sup> This was a typical case of gonococcal endocarditis, and was reported as such. It is included here because a non-hemolytic anaerobic streptococcus was also constantly present in the blood cultures.

TABLE I—Continued

Author	Number of Cases	Underlying Heart Disease	Specific Treatment	Reference
CHURCHILL, A.	1	Rheumatic, mitral	Sulfanilamide	Jr Am Med Assoc, 1940, cxv, 1357
DOUGLASS, J. C.	1	Rheumatic, mitral	Sulfapyridine and heparin	New Internat Clin, 1940, iv, Ser 3
CUTLER, L. T.	1	Rheumatic, mitral	Sulfanilamide and sodium cacodylate	Jr Mich. State Med Soc, 1940, xxxix, 946
CRAGG, F. S., and POSTON, M. A.	1	Rheumatic, aortic, ?mitral	Sodium sulfapyridine	North Carolina Med Jr, 1941, ii, 24
SEYMOUR, H. A.	1	Rheumatic, mitral	Sulfanilamide and intravenous typhoparatyphoid vaccine	New York State Jr Med, 1941, xli, 45
	3	Rheumatic, mitral and aortic	Sulfapyridine and intravenous typhoparatyphoid vaccine	
LICHSTEIN, S. S., and BIRMAN, W.	1 1	Rheumatic, mitral (a) —	Sulfapyridine and heparin Sulfanilamide and sulfapyridine and heparin (a)	Jr Am Med Assoc, 1941, cxvi, 286
BIRMAN, W., and BAUER, G.	1 1	Rheumatic, mitral —	Radiotherapy, sulfanilamide and hyperthermia Sulfanilamide and hyperthermia	Jr Am Med Assoc, 1941, cxvi, 292
MURPHY, J. L.	1	Patent ductus arteriosus	Surgical closure	Weekly Bull St Louis Med Soc, 1941, xxxv, 304
HEVLY, H. E., and HICK, F. K.	1	Coarctation of the aorta	Sulfanilamide	Ann Int. Med, 1941, xv, 291
WINTER, F. PARKER	1	Rheumatic, mitral	None	Lancet, 1941, i, 630.
DATCHEVANS, J. S.	1	Rheumatic, mitral	Neosarsphenamine, sulfapyridine, sulfamethylthiazole and heparin	Jr Am Med Assoc, 1941, cxvii, 101.

(a) This patient, treated by the author (S. R. K.), is listed also in table 2, as case 2

(b) The authors did not consider that heparin used in the therapy of this patient had had an appreciable effect on blood coagulation

TABLE I—Continued

Author	Number of Cases	Underlying Heart Disease	Specific Treatment	Reference
JENSEN, M	1	Rheumatic, mitral	Sulfamethylthiazole	Ugesk f Laeger, 1941, cii, 1261
BOURNE, G, KEEFE, K D, and LUBBS, O S	1	Patent ductus arteriosus	Surgical closure and sulapyridine	Lancet, 1941, ccxi, 444
LEACH, C E, ET AL	1	Patent ductus arteriosus	Sulfapyridine, heparin and sulfathiazole (6)	Jr Am Med Assoc, 1941, cxvii, 1345
	1	Rheumatic, aortic	Sulfathiazole	
GROSS, R E	2	Patent ductus arteriosus	Sulfonamides and surgical closure	Modern concepts of cardiovascular disease, 1941, No 12, 10 (Dec)
FIELD, H, JR, HOONLER, S W, and AVERY, N L, JR.	1	Tetralogy of Fallot	Sulfapyridine	Am Jr Med Sci, 1941, cci, 798
BICKFELT, G, and MOYER, J J	1	Rheumatic, mitral	Sulfathiazole	Rev Med de la Suisse, 1941, lxi, 474
TOUROFF, A S W, VESSELL, H, and CHASSANOFF, J	1	Patent ductus arteriosus	Surgical closure	Jr Am Med Assoc, 1942, cxviii, 890
OSGOOD, L E	3	—	Neosarsphenamine, or neoarsphenamine and sulfathiazole	Arch Int Med, 1942, lxi, 746
SMITH, C, SAULS, H. C, and STONE, C F	1	Patent ductus arteriosus	Sulfanilamide	Jr Am Med Assoc, 1942, cxix, 478
TOUROFF, A S W, and LUCHMAN, L R	1	Patent ductus arteriosus	Surgical closure	Am Heart Jr, 1942, xxiii, 847
CHRISTIE, A, and PARKER, A	1	Congenital	Sulfanilamide and sulfathiazole	Clinics, 1942, i, 677
HUMPHREYS, G H	1	Patent ductus arteriosus	Surgical closure	Surgery, 1942, vii, 841
	1	Patent ductus arteriosus	Sulfonamide and surgical closure	

(6) Six months after disappearance of all evidence of infection and one month after discontinuance of therapy in this patient, the ductus arteriosus was closed surgically by Dr Robert E. Gross. Four months later, the patient was killed in an automobile accident, and autopsy revealed complete healing of the bacterial lesion.

TABLE I—Continued

Author	Number of Cases	Underlying Heart Disease	Specific Treatment	Reference
DUTTON, A B, and FINKSBOG, G E	1	Patent ductus arteriosus	Sulfadiazine and surgical closure	Yale Jr. Biol and Med, 1942, xv, 259
WILSON, W A, HERRICK, C F, and SANDERS, J M	1	Patent ductus arteriosus	Sulfapyridine and heparin	Ann Int Med, 1943, xviii, 242
LOTROP, A S W	3	Patent ductus arteriosus	Surgical closure	Am Heart Jr, 1943, xxv, 187
HARRINGTON, S W	1	Patent ductus arteriosus	Surgical closure	Proc Staff Meet Mayo Clin, 1943, xviii, 217
GROSS, R F	3	Patent ductus arteriosus	Surgical closure	New York State Jr Med, 1943, xliii, 1856
ALTON, J W, BOWENKAMP, W. W., JR., and ROSS, O	1	Patent ductus arteriosus	Surgical closure	Ann Int Med, 1943, xiv, 1003
LEWIS, I, ROSSIGNOLAT, P, GREEN, H J, and RUSSELL, M	2 2 2	Rheumatic, mitral Rheumatic, aortic Rheumatic, mitral and aortic (m)	Penicillin and heparin (m)	Jr Am Med Assoc, 1944, cxxiv, 144
DUNN, M H, and HANNA, G L	2	Rheumatic	Penicillin	Jr Am Med Assoc, 1944, cxxiv, 611
BROWN, W H	1 1	Rheumatic, aortic Patent ductus arteriosus	Sulfathiazole Sulfathiazole and sulfadiazine	Jr Am Med Assoc, 1944, cxxv, 1023

\* All these patients had been given sulfonamide therapy previously, one also received sulfonamides between courses of penicillin and heparin, and were treated for a time during the administration of these drugs.  
 † One of these cases, though caused by a hemolytic streptococcus, showed a subacute rather than an acute course

Cases of streptococcal endarteritis of the patent ductus arteriosus treated by operative closure, it is seen, hold an impressive place on the list of apparent recoveries, quite disproportionate to their relative frequency (five of the 250 cases of subacute bacterial (streptococcal) endocarditis and endarteritis collected by the author and White<sup>1</sup>) Surgical technic has progressed to make this procedure relatively safe and sure, giving a high percentage of apparent cures The stimulating questions of the mechanisms of recovery in these cases and of the possible prophylactic value against bacterial endarteritis of ligating the non-infected ductus are discussed elsewhere<sup>1</sup>

### SULFAPYRIDINE IN SUBACUTE BACTERIAL (STREPTOCOCCAL) ENDOCARDITIS

Of the methods of treatment noted in our own experience, sulfapyridine proved the most active in lowering the temperature\* and in producing negative blood cultures† Except in the four instances cited among the 197 treated cases, however, its effects were no more than transient The failures of the drug to cure appear related to the following factors

- 1 Death occurs at times from embolism or congestive heart failure in spite of even a strong action of the drug in controlling the infection
- 2 Rarely, toxic effects of the drug itself are fatal‡
- 3 The action of drugs of this group is bacteriostatic, rather than bactericidal, and they require phagocytes for the final killing of the organisms The paucity or absence of polymorphonuclear leukocytes in proximity to the

\*Some have called this drop in temperature only an "antipyretic effect," implying that sulfapyridine reduces fever in this disease solely by an action on the temperature-regulating center and not by any direct bacteriostasis of streptococci This response, however, parallels other evidences of effectiveness of the drug it has occurred, in most cases strikingly from the start, and has been sustained in our patients who, with the additional use of heparin, have gone on to recovery, in others, it has been absent, slight, or transient, except in those who have responded as well as the group just noted, remaining afebrile and culture-negative for as long as two months, but have received no heparin and "escaped" from the sulfapyridine effect Fall in temperature is the rule with the disappearance of bacteremia following medication, if fever recurs, one can foretell that blood cultures again will be found positive (unless the pyrexia has another cause embolism, drug sensitivity rarely, intercurrent infection like nasopharyngitis not responding to the drug, etc.) Swan<sup>11</sup> and Orgain and Poston,<sup>12</sup> moreover, have shown a definite correlation between the in vitro bacteriostatic power of the sulfonamides on strains of *Streptococcus viridans* and their effectiveness in treatment (including reduction of fever) Sulfapyridine acts strongly on many of these strains, and in bacterial endocarditis, as in pneumonia and meningitis, fall in temperature is a prime index of the response to specific therapy

†This is true sterilization of the blood stream, and not merely inhibition of the growth of organisms in the culture media by drug present in the drawn blood, for at no time in our experience has the addition of potassiumbenzoic acid secured positive cultures when cultures were negative without it

‡Sometimes grave side-actions of the drug make its continuance impossible More often, disagreeable and perhaps injurious but less severe toxic effects are the reason for omitting the drug, as stressed below, failure to persist in administering sulfapyridine in the combined therapy with heparin in the face of any but the most serious side-effects has sacrificed the chance of possible cure

bacteria within the vegetations makes this a decisive factor in the treatment of this disease †

4 The drug may penetrate in insufficient concentration to the organisms within the bacterial vegetations. Duncan and Faulkner<sup>14</sup> found that sulfapyridine fails to enter blood clot in vitro, but Uhley and Katz,<sup>15</sup> on the contrary, demonstrated that it does permeate through a fibrin barrier ‡. Results of such test-tube experiments with these structures, similar to but not identical with bacterial vegetations, may or may not have validity within the living body. Vegetations, it must be remembered also, constantly are being worn down and laid open by embolization. The problem of contact of drug with organisms can not be considered as settled; the phenomenon of acquired resistance (see 6, below) and the occurrence of recoveries with the use of the drug alone or in combined therapy show that contact does occur, but it is likely that it is variable, and may be much restricted. As pointed out,<sup>40</sup> the presence in the vegetation of tissue debris, shown by Lockwood and his co-workers<sup>16a</sup> to inactivate sulfonamides, also may decrease the "effective concentration" of the drug.

5 Some strains of non-hemolytic streptococci fail to respond to the action of the drug from the start of treatment. Swain,<sup>11</sup> Poston and Orgain,<sup>17</sup> and others have shown that the many different strains of these organisms vary widely in susceptibility to the bacteriostatic action of sulfapyridine and related drugs. One or more sulfonamides inhibited the growth in vitro of 17 among 25 strains of *Streptococcus viridans* which Poston and Orgain tested, but against eight no drug was active. These drugs are particularly ineffective against the enterococci.<sup>18</sup>

6 Other strains of non-hemolytic streptococci, susceptible to sulfapyridine from the beginning of treatment, later become resistant to its action. In all but four of the cases which had shown an initial response to sulfapyridine, fever and bacteremia, as noted, recurred in from a few days to two months. This clinical "escape" from sulfapyridine effect, which Whitby<sup>19</sup> pointed out in the disease, was stressed early by the present author.<sup>12, 20</sup>

In 1938, Cokkinis and McElligott<sup>21</sup> observed that when patients with gonorrhea were treated with inadequate dosages of sulfanilamide, or particularly, when the drug was discontinued too early, the relapses which followed were highly refractory to further treatment with sulfanilamide. They

† The problems involved in treatment are discussed in another publication.<sup>12</sup>

‡ Friedman<sup>14</sup> found limited penetration of sulfapyridine and sulfanilamide through fibrin-platelet membranes in vitro. Fibrin-platelet masses infected with *Streptococcus viridans* and placed in permeable capsules implanted within the abdominal cavity of rabbits were not sterilized by prolonged intravenous and intraperitoneal administration of sodium sulfapyridine or sulfanilamide. These experiments, however, did not actually determine the in vitro penetrability of fibrin-platelet masses by the drug, for the drug likewise failed to sterilize a fibrin clot but had but little effect on the growth of organisms placed directly in the absence of fibrin-platelet masses—in such filter-capules within the peritoneal cavity. Only a small amount had been added to the capsules before their implantation and the elements of a bacteriostatic effect by a concentration of drug within the capsules were not determined.

named this phenomenon "acquired resistance." Its mechanism was clarified by the demonstration<sup>22, 23, 24, 25</sup> that organisms could be made insusceptible to the sulfonamide drugs. Pneumococci sensitive to sulfapyridine, for example, were rendered markedly resistant by growing them in the presence of increasing concentrations of the drug in vitro, or passing them through series of mice given less than curative amounts of sulfapyridine. The resulting "fast" organisms were unchanged in morphology, virulence, growth away from the drug, type specificity, and susceptibility to serum<sup>23, 26</sup>. Resistance can be lost when only partially developed, Schmidt and his associates found, but when established it persists almost indefinitely, having remained for 200 passages through untreated mice<sup>28</sup>. Organisms rendered resistant in vitro remain so in vivo, and conversely<sup>26</sup>. Pneumococci made resistant to one sulfonamide are resistant also in vitro and in vivo to other sulfonamides<sup>25, 26, 27, 28, 29</sup>. \* Different strains of an organism varied in their ability to develop fastness,<sup>29</sup> and an individual strain acquired resistance to the various drugs at different rates, doing so most rapidly to the least effective and least rapidly to the drug with the greatest effect<sup>29, 30</sup>.

Schmidt and Sesler<sup>31</sup> concluded that sulfonamide-resistant forms result from an action of the drug on the sensitive organisms, and not from the normal multiplication of such organisms. MacLeod<sup>32</sup> showed early that alterations in the intermediary metabolism of the bacteria accompany the development of fastness, with a marked decrease in the production of hydrogen peroxide and in the oxidation of glycerol, pyruvate, and lactate. He later<sup>33</sup> demonstrated that these resistant organisms synthesize increased amounts of sulfonamide inhibitor. Mirick<sup>34</sup> identified this as paraaminobenzoic acid, of which, he found, resistant pneumococci produce 10 times as much as do the parent strains. Resistant staphylococci, Landy and his group showed,<sup>35</sup> elaborate this inhibitor in 70 times the usual amounts, and continue to produce a great excess.

That sulfonamide-sensitive organisms may become sulfonamide-resistant in the course of clinical treatment has been demonstrated repeatedly. In a case of pneumococcal meningitis treated with sulfapyridine,<sup>36</sup> for example, and in one of type VII pneumococcal endocarditis treated with sulfapyrazine,<sup>37</sup> both of which had shown an early response to the drugs and a later absence of effect, in vitro tests showed the initial organisms susceptible to the respective drugs, but those isolated after therapy to be resistant. Lowell,

\* Clinically, we have seen responses to sulfapyridine after the development of resistance to other sulfonamides, but the latter drugs have been ineffective following sulfapyridine "escape." This accords with the finding by Kirby and Rantz<sup>28</sup> that the degree of resistance correlates directly with the bacteriostatic power of the drug. Apparently sulfapyridine, the more active drug, could overcome the lesser resistance imparted by the less active drugs, but their bacteriostatic power was insufficient to overcome the greater fastness which it had produced. In our experience, increasing the blood concentration of sulfapyridine after infection had become resistant to a given level resulted at times in reducing the temperature—especially with very high concentrations—but never produced sterilization of the blood stream. This is at variance with the finding by the above authors that organisms resistant to lower concentrations of a drug may be susceptible to higher levels, but accords with earlier observations.



Strauss, and Finland <sup>25</sup> found type II pneumococci isolated from each of two patients at the beginning of pneumonia therapy to be highly sensitive to sulfapyridine, and to sulfathiazole and sulfamethylthiazole, after relapse had occurred in one patient during sulfapyridine therapy and in the other shortly after discontinuing this drug, the organisms then isolated were found highly resistant in vitro to all three drugs. In a case of type VII pneumococcal pneumonia, <sup>28</sup> the bacteria, originally sensitive, became resistant to sulfadiazine during treatment, transmitted by contact to a second patient, they produced pneumonia which also was resistant to sulfadiazine, and both patients were shown later to carry in their throats these virulent sulfadiazine-fast pneumococci. In one report of striking interest, <sup>30</sup> endocarditis developed in a horse during immunization with type A hemolytic streptococci for the production of antistreptococcal serum. Sulfanilamide failed to overcome the bacteremia, and the animal died on the eleventh day of treatment. Streptococci from the blood showed a progressive increase of resistance to sulfanilamide, and those isolated the day of death were much more resistant than the stock culture. Organisms from the valvular vegetations were less resistant than these last ones from the blood, but more so than the original strain, a finding which was explained by the lower concentrations of drug to which these organisms in the vegetations were exposed, as compared to those in the blood stream.

Hamburger and his co-workers <sup>40</sup> conclude that resistance is most likely to develop when the nature of the lesion prevents complete eradication of the bacteria, yet permits limited exposure to the drug. Endocarditis provides ideal conditions for this, they point out, organisms can become moderately resistant from contact with the lower concentration of drug within the vegetations, enabling them to survive in the higher levels in the blood stream, contact with which, in turn, produces even greater fastness. Resistant pneumococci arise infrequently, they state, during brief treatment, such as is usual in pneumonia, but in prolonged treatment, as in endocarditis, they appear to develop regularly. In treating subacute bacterial (streptococcal) endocarditis, we have found "acquired fastness" to take place almost invariably, often after even brief medication. In the use of sulfapyridine alone, and—as will be noted presently—in combined therapy, it is a phenomenon of the first importance.

### HEPARIN AND CHEMOTHERAPY IN SUBACUTE BACTERIAL (STREPTOCOCCAL) ENDOCARDITIS

In November 1939 the author and White introduced a new method of treatment of subacute bacterial endocarditis, using heparin and chemotherapy in combination.<sup>41</sup> We employed heparin, a powerful anticoagulant which had been shown to arrest the deposition of platelets and fibrin, in an attempt to prevent further thrombotic deposits on (and in) the vegetation. This could restrict the nidus and culture medium for bacterial growth, and

prevent embolism from the detaching of fresh thrombus, particularly, checking the enlargement of the vegetations could enable the fibroblasts present at their base to heal the areas thus limited. There was no evidence that heparin could dissolve the vegetations, or that it could increase their permeability to sulfapyridine (the chemotherapeutic agent used), except as reduced platelet and fibrin deposition itself might have this effect.

We emphasized the *combined* nature of this new attack, and the necessity of an accompanying strong action of the chemotherapeutic drug<sup>18, 20</sup>. Further experience has stressed this still more forcibly. Without such an accompanying action, heparin has not been curative, even when administered for as long as three weeks (or, as in one reported case,<sup>10</sup> for six), it has been useful only in those cases in which sulfapyridine (or a related drug) was able to reduce the temperature to normal or near it and to sterilize the blood stream. Some have questioned the value of heparin, when the chemotherapy of itself can produce this result, and heparin can not. Yet—and this is the crucial point—sulfapyridine frequently (and related drugs less often) abolishes fever and bacteremia, even for two months, but when it is discontinued, or, usually, as it is being given, these manifestations of active infection almost invariably recur, and recovery has rarely taken place. If, however, blood coagulability has been decreased during such a period (two weeks, or at times less) of strong bacteriostatic response to a sulfonamide, recovery—with but one exception in our experience—has resulted.

Heparin, we have found, has regularly produced the desired decrease of blood coagulability\*. The great problem has been in securing the accompanying antibacterial effect. Some strains of non-hemolytic streptococci, as noted, are insusceptible to sulfonamide action from the start, but—more significant because it is preventable—previous medication during the present illness had rendered the streptococci of many patients drug-resistant. If sulfapyridine had already been given and "escape" had occurred (and frequently if the drug had been discontinued while still active), its further use as a rule produced but little effect, at times the temperature could be lowered, especially by very large doses, but blood cultures rarely could be rendered negative. If the organisms failed to respond to sulfapyridine, moreover, we have never obtained later adequate responses to other sulfonamides†. Most striking and regrettable were the cases which had excellent

\*I have not used dicoumarol in the combined therapy, or known of its use when the accompanying bacteriostasis has been strong. Though having the convenience of oral administration, dicoumarol lacks the responsiveness to control of heparin—a long latent period, 24 hours or more, elapses before it becomes effective, and its action passes off gradually after it has been discontinued. Several investigators have stressed its toxic actions, particularly in causing bleeding.

Intracranial hemorrhages have been described with the use of heparin in this disease, and we have seen them take place during heparinization in three of 40 patients. Cerebral deaths occur commonly, however, as a complication of the endocarditis itself, as a result of embolism, the frequency of such deaths has not been increased in our patients under heparin therapy. This problem will be discussed in a later article.<sup>21</sup>

†Satisfactory responses to sulfapyridine have been seen, however, following "escape" from the action of other sulfonamide drugs.

responses in the past, but which were found resistant to further medication when brought to us for combined therapy\*. If this treatment was contemplated, it was most important to withhold sulfapyridine until both drugs could be given; even in small amounts and for brief periods, it apparently could produce fastness, and all chance of success was lost. In patients previously untreated with sulfapyridine, approximately one-half gave the desired bacteriostatic response. The first rule of success with the combined therapy, then, has been the avoidance of the previous use of sulfapyridine. The second rule has been the persistent continuance of treatment, even in the face of all but the most dangerous toxic effects of the sulfapyridine and of grave turns of the disease itself. Repeatedly we have observed all chance of cure sacrificed by interrupting or discontinuing sulfapyridine at a time of good response (or before its effect could be shown) because the patient developed nausea and vomiting, a skin rash, or a falling erythrocyte count. In some of our patients, now living and well more than two years later, we pressed on with treatment even though intractable vomiting demanded medication and glucose solutions by vein and morphine in narcotic doses, or—in one striking instance (table 2, case 7)—despite continuous severe hematuria from renal concretions of sulfapyridine, necessitating blood transfusion.

Of our originally reported group of patients, two are listed among the apparent recoveries noted in table 1. In the first of these, all evidence of *Streptococcus viridans* endocarditis disappeared following sulfapyridine-heparin therapy, but a concurrent rheumatic infection persisted and the patient died in congestive heart failure six months later. Autopsy disclosed acute and chronic rheumatic endocarditis and myocarditis, and completely healed calcified and fibrosed vegetations of bacterial endocarditis, free of streptococci, on the mitral valve. The second patient has remained well and active except for an attack of rheumatic fever in 1944. She has shown no evidence of bacterial endocarditis for over five years now, since completion of therapy on May 26, 1939.

Table 2 presents 10 additional apparent recoveries among the 34 patients with subacute bacterial (streptococcal) endocarditis, treated subsequently with heparin and chemotherapy by the author. All were clinically definite cases, having had two blood cultures positive for *Streptococcus viridans* in two instances and three or more in the others. In patient 1, in whom all manifestations of the disease disappeared following therapy, with restoration of vigorous well-being and a gain of 46 pounds in weight, bacterial endocarditis recurred directly after the removal of two abscessed teeth three months later, and treatment then was unavailing. Postmortem examination showed beaked and fresh vegetations which confirmed the clinical belief that

TABLE II  
Further Apparent Recoveries among 34 Patients with Subacute Bacterial (Streptococcal) Endocarditis Treated by the Author with Combined Chemotherapy and Heparin

No	Patient	Age Sex	Duration of Infection	Underlying Heart Disease	Specific Treatment	Treatment Completed	Outcome
1	W E D	33 M	4 mos	Rheumatic, aortic	Sulfapyridine and heparin *	March, 1940	Well, active and without evidence of disease after completion of therapy, with 46 lb gain in weight. Reinfection directly followed extraction of two abscessed teeth three months later. Autopsy showed healed and fresh lesions of subacute bacterial endocarditis.
2	J Z	33 M	5 mos	Rheumatic, mitral	Sulfapyridine and heparin	April, 1940	Well, active and without evidence of disease since completion of therapy.
3	L B	30 F	4 mos	Rheumatic, mitral	Sulfapyridine and heparin	June, 1940	Well, active and without evidence of disease since completion of therapy.
4	L L	45 M	1½ mos	Rheumatic, mitral	Sulfapyridine, sulfadiazine and heparin	March, 1941	Well, active and without evidence of disease after completion of therapy. Sudden death, when no evidence of infection was present, on July 25, 1943.
5	G B	30 F	1 mo	Rheumatic, mitral	Sulfapyridine and heparin	Sept., 1941	Well, active and without evidence of disease since completion of therapy.
6	P. V	31 M	5 mos	Rheumatic, mitral	Sulfadiazine and heparin	Dec 1941	Well, active and without evidence of disease since completion of therapy.
7	G P	22 F	2 mos	Rheumatic, mitral	Sulfapyridine and heparin	March, 1942	Well, active and without evidence of disease since completion of therapy.
8	B P	19 M	1 mo	Rheumatic, mitral	Sulfapyridine and heparin	April, 1942	Well, active and without evidence of disease since completion of therapy.
9	G A	29 F	2 mos	Rheumatic, mitral and aortic	Sulfapyridine and heparin	April, 1942	Well, active and without evidence of disease since completion of therapy.
10	L L	40 M	5½ mos	Rheumatic, mitral and aortic	Penicillin, sulfadiazine and heparin	Nov 1943	Well, active and without evidence of disease since completion of therapy.

Some of this investigation was aided by a grant from the Dazian Foundation for Medical Research and grants from Roche-Organon, Inc. Cases 5 through 9 were treated with the assistance of Dr —now Lt —Charles Ressler of New York. In this and most of the following cases sulfapyridine was given in part by vein, as sodium sulfapyridine.

the patient had had a second attack of the disease, precipitated by dental extraction, after he had recovered from his original infection. Patient 4 remained well and active following completion of therapy and showed no further evidence of the disease. Twenty-eight months later, while up and about and feeling perfectly well, he suddenly collapsed and was dead within a few minutes. There was no autopsy. Except for this patient, cases 2 through 9, it is seen, have remained well now from over two years to more than four years. Case 10, treated more recently (November 1943), is discussed later in this paper (page 91). These cases will be presented in full in a further report<sup>41</sup> dealing with the results, principles, and technic of therapy.

Conservation of the bacteriostatic effect of sulfapyridine for its use at the time of heparinization, and greater persistency in the administration of the drugs can increase the proportion of recoveries from this combined method of therapy. Improvements in technic, too, may do so. Further progress lies particularly in the development of sulfonamide or other drugs which are more active than sulfapyridine against the strains of non-hemolytic streptococci and effective against more of these strains, and which are less toxic. To date, no newer sulfonamide drugs have been found to possess these superiorities\*. Another chemotherapeutic agent, however, of different origin and mode of action—penicillin—now holds much promise in the treatment of this disease.

#### PENICILLIN IN SUBACUTE BACTERIAL (STREPTOCOCCAL) ENDOCARDITIS

The keenest of interest in the treatment of subacute bacterial endocarditis now centers about penicillin. In his original description of the substance, Fleming<sup>42</sup> listed the *Streptococcus viridans* among the organisms sensitive to its action, and later workers<sup>43, 46, 47, 48</sup> have confirmed this in vitro antibacterial effect. Bornstein<sup>45</sup> found that penicillin inhibited each of 13 cultures of *Streptococcus viridans*, including three isolated from endocarditis patients, though against 27 strains of enterococci he found it ineffective, as had Fleming. Heilman and Herrell<sup>44</sup> showed that three strains of *Streptococcus salivarius* were totally inhibited in tissue culture by penicillin in concentrations of 40 micrograms per cubic centimeter (the order of sulfonamide inhibition). Dawson and his co-workers<sup>49</sup> compared the in vitro sensitivity to penicillin of strains of non-hemolytic streptococci from bacterial endocarditis cases with that of a standard strain of hemolytic strepto-

coccus Of 41 such strains (17 of them *viridans*), they found one twice as sensitive, eight equally sensitive, 23 one-fourth to one-half, four one-eighth, two one-sixteenth, and one one-sixty-fourth as sensitive as the standard, and only two—one of them being one of two strains "resembling enterococci"—resistant The sensitivity of a strain, they found, was not correlated with its cultural or serological properties

Several reports<sup>49, 51, 52, 53</sup> of the use of penicillin in subacute bacterial (streptococcal) endocarditis indicate a reduction of fever and sterilization of the blood, but in nearly all cases fever and bacteremia have recurred on discontinuing the drug A patient of Herrell's,<sup>51</sup> for example, infected with a *Streptococcus viridans* inhibited in vitro in dilutions of 1 500,000 of penicillin, became afebrile and culture-negative six hours after beginning a constant intravenous drip of the drug, cultures continued negative during the six days of administering 128,000 units, but four to six hours after completing therapy bacteria reappeared in the blood Of 10 *Streptococcus viridans* cases which Dawson treated with penicillin, five, given very small amounts, in preliminary trials, showed no significant results, and a later patient with doses believed insufficient (a total of 975,000 units for three interrupted periods of five days each), was not benefited Treatment failed in another, despite almost eight million units over 33 days, the blood cultures, temporarily negative, were positive at the time of death from cerebral embolism Two patients, given 830,000 units over 10 days and 1,420,000 units over 23 days, however, were reported as alive and well for 13 and nine months, respectively, after discontinuing therapy In one case of exceptional interest, the infection responded to penicillin on every one of numerous occasions, but recurred within two or three weeks after each discontinuance of the drug, and persisted after nearly seven million units had been administered In a report for the Committee on Chemotherapeutic and Other Agents of the National Research Council, Keefer<sup>54</sup> stated that of 17 cases of bacterial endocarditis (organisms unspecified) treated with amounts from 250,000 to 1,760,000 units, over nine to 26 days, there were deaths in four, no appreciable effect in ten, and temporary improvement in three, of which two relapsed soon after stopping therapy Later, Keefer<sup>55</sup> stated that of 55 treated cases only three were alive after one year of study He mentioned other patients whose disease persisted after more than twenty million units of the drug

The variations—indicated in the previously-mentioned tests—in susceptibility of different strains of *Streptococcus viridans* to penicillin, as to sulfapyridine, probably are a factor in the failures of penicillin Acquired resistance to the action of penicillin, too, may perhaps be a second factor Abraham and his co-workers<sup>56</sup> first demonstrated that organisms (*Staphylococcus aureus*) could be rendered fast to penicillin by growing them in broth with increasing amounts of the drug; Rammelkamp and Maxon<sup>57</sup> confirmed this, and showed that penicillin clinically may produce resistant strains, for

in four of 14 subjects, the *Staphylococcus aureus* isolated following treatment was much less sensitive to the drug than that cultured prior to it. These workers observed, significantly, that the development of penicillin fastness required prolonged exposure, contrasting with the readiness with which sulfonamide fastness results. Powell and Jamieson<sup>58</sup> found penicillin highly effective in mouse experiments against both parent and sulfapyridine-fast strains of pneumococci. Schmidt and Sesler<sup>59</sup> showed the converse: rendering pneumococci resistant to penicillin does not change their response to sulfapyridine. This absence of cross-resistance in either direction may hold important implications for future therapy of subacute bacterial endocarditis. These last authors produced penicillin fastness by serial passage of two strains of pneumococci through treated mice, and in one this persisted for 30 passages through normal mice, in vitro resistance accompanied that in vivo. McKee and Houck,<sup>60</sup> who developed fastness in hemolytic streptococci also and raised the resistance of staphylococci in vitro to 6,000 times that of the parent strain, found that penicillin-fast organisms show a proportionate decrease in virulence for mice—unlike sulfonamide-fast bacteria, which are unchanged in virulence. To Dawson and Hobby,<sup>49</sup> this finding makes penicillin-fastness much less significant, they regard clinical resistance as relatively rare, also, since it occurred in but one possible instance among their 100 cases, many "given prolonged therapy." Certainly there was no suggestion of resistance in their patient whose temperature fell and cultures became negative on each of the many resummptions of penicillin; with sulfapyridine such repetitive responses are exceedingly rare.

As with the sulfonamide drugs, the mode of action of penicillin bears importantly on its effects in subacute streptococcal endocarditis. Most evidence indicates that it is bactericidal as well as bacteriostatic<sup>47, 48, 51, 52</sup>, unlike the sulfonamides, which reduce the rate of bacterial multiplication, penicillin causes an actual decrease in their number, an effect, moreover, not dependent on phagocytosis.<sup>51</sup> It has been shown, however,<sup>49, 51</sup> that the drug fails to sterilize cultures completely, and that 1 to 4 per cent of the organisms survive. Dubos<sup>53</sup> states: "When the susceptible organisms which have been exposed to the drug are transferred to a new medium free from it, they grow as readily as untreated cells." The growing out of such surviving organisms may account for the recurrence of active infection after withdrawal of penicillin.

The ability of penicillin to penetrate bacterial vegetations has not been investigated. Rammelkamp—who with Kellner<sup>54</sup> found that the drug failed to penetrate red blood cells in significant amounts (usually less than 10 per cent of the concentration in plasma)—believes that it does not penetrate the vegetations of subacute bacterial endocarditis (though it may enter the soft vegetations of the acute form).<sup>55</sup> To him, the presence of organisms in relatively avascular tissue is the chief obstacle to penicillin therapy in the

In treating subacute bacterial (streptococcal) endocarditis with the sulfonamides and heparin, we found that if the chemotherapeutic agent could maintain a strong antibacterial effect, with sterilization of the blood and reduction of the temperature to normal or near it, during the period of decreased blood coagulability, recovery would result. If penicillin could produce a similar strong antibacterial effect, we believed that its use in place of a sulfonamide in the chemotherapy-heparin method might result in similar success. We began such treatment with the combination of penicillin and heparin on a patient with *Streptococcus viridans* endocarditis (table 2, case 10) on November 17, 1943. His temperature fell gradually to normal and the culture plates were cleared of bacterial growth, streptococci continued to appear in the broth, however, though they had become pleomorphic, poorly-staining, and strikingly reduced in size. Because of this failure to secure full antibacterial effect, sulfadiazine was also given, in the hope that the additive action would be effective. The patient received 1,900,000 units of penicillin, given during the first seven and one-half of the 10 days of heparinization, and a total of 23 grams of sulfadiazine administered during the last four days. After the use of sulfadiazine, blood cultures became negative in the broth as well as on the plates, and since the discontinuance of all therapy on November 27, the patient has been free of evidence of bacterial endocarditis and remains well and active.

Loewe and his associates have reported six cases of streptococcal endocarditis treated with apparent recovery by combined penicillin and heparin (table 1)<sup>60</sup>. Their patients received from 1,400,000 to 7,890,340 units of penicillin, averaging 4,706,390 units, for periods of 13 to 51 days, with an average of approximately 31 days. In three of the patients, two, three, and four courses of treatment, respectively, were given because of continuing fever or positive blood cultures or both.

Much further experience is needed to determine the value of penicillin in subacute bacterial (streptococcal) endocarditis, and to learn its optimal dosage and plan of administration. It holds a clear advantage over sulfapyridine in its relative freedom from toxic effects (permitting high dosage), and its lesser tendency to induce bacterial resistance, but data are yet insufficient for comparing the two otherwise. In some cases, as in our own, a sulfonamide may valuably supplement its effect. Two questions in particular remain to be answered. Can penicillin, with its superiorities and its different mode of action, of itself result, unlike sulfapyridine in a high proportion of successes in this disease? Is the accompanying use of heparin of real benefit with penicillin—which now seems likely—as it is with sulfapyridine?

#### SUMMARY AND CONCLUSIONS

1. In a large series of cases of subacute bacterial (streptococcal) endocarditis, sulfanilamide, sulfathiazole, and sulfadiazine at times gave transient



benefit, but resulted in no recoveries. Sulfapyridine reduced the fever in a majority and frequently rendered blood cultures negative, but cured only four of 197 patients. Neoarsphenamine, the sulfonamides together with intravenous typho-paratyphoid vaccine or with hyperthermia, and various other measures gave no lasting help.

2 Apparent recoveries from subacute streptococcal endocarditis reported since 1939 have been analyzed, and are listed in table 1. Because of their uncertainty, some cases reported as cured could not be included. A method of therapy is not fairly tested, it is pointed out, when the described technique has not been followed or is used with lack of care or persistency, and statistics based on such cases are misleading. Instances of endarteritis of the patent ductus arteriosus treated by surgical closure appear prominently in the list.

3 Sulfapyridine proved to be the most active of the drugs in lowering the temperature—not a mere “antipyretic” effect—and in rendering blood cultures negative—a sterilization of the blood stream—but its benefits passed off in a few days to two months. The failures of sulfapyridine to cure appear related to complications of the disease, toxic effects of the drug, its bacteriostatic rather than bactericidal mechanism, a low concentration of drug within the vegetations, its ineffectiveness against some strains of non-hemolytic streptococci, and the almost regular development of resistance to its action. Such clinical “escape” from sulfonamide effect after an earlier response has been shown to result from a decreased susceptibility of the bacteria themselves.

4 The author and White introduced heparin, in combination with chemotherapy in subacute bacterial endocarditis, in an attempt to prevent the further deposition of platelets and fibrin on the bacterial vegetations. The *combined* nature of this attack is again stressed. Heparin has been beneficial only when sulfapyridine (or a related drug) reduced the temperature to normal or near it and sterilized the blood stream. Decreasing the blood coagulability during a period of such antibacterial effect has almost regularly resulted in recovery. Avoidance of the previous use of sulfapyridine, because of the readiness with which fastness develops, and the persistent continuance of treatment have been the two rules of success with this method. In addition to two in the original series, 10 further apparent recoveries from the disease treated by the author are noted (table 2).

5 Penicillin effective in vitro against non-hemolytic streptococci, can reduce the temperature and sterilize the blood in cases of subacute bacterial (streptococcal) endocarditis, but on discontinuing the drug, fever and bacteremia have recurred in all but two of such patients (those of Davson) reported to date. Lesser effectiveness of penicillin against some strains of the organism, possible acquired bacterial resistance and inadequate penetration into the vegetation, and the failure of the drug (although bactericidal with a bacteriostatic) completely to sterilize, appear as factors in its unsatisfactory results.

6 Substituted for sulfapyridine in the heparin-chemotherapy method, penicillin was partially effective in a personally-treated case, but pleomorphic streptococci persisted on the culture plates, these disappeared with supplemental sulfadiazine, and the patient has remained well since completing the 10 day course of treatment in November 1943. Loewe's group has reported six apparent recoveries from streptococcal endocarditis with the use of penicillin and heparin. Penicillin excels sulfapyridine in its low toxicity and lesser tendency to induce drug fastness, but further data are needed to evaluate its effectiveness, to determine the best plan of therapy, and to learn if, unlike sulfapyridine, penicillin can alone result in a high proportion of successes, and if accompanying it also the use of heparin is advantageous.

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# A CLINICAL STUDY OF RHEUMATIC PERITONITIS <sup>3</sup>

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THE appearance of four cases of rheumatic peritonitis at the Richmond Memorial Hospital recently served to bring attention to this infrequently discussed subject. Rheumatic fever causes inflammatory changes in and about the synovial membranes and it has long been known that other serous membranes may show similar involvement. Of these, pericardial disease is most common. Rheumatic pleuritis has been frequently described and is recognized clinically in many instances of acute rheumatic fever.

The occurrence of a similar reaction in the peritoneum coincidental with or preceding acute rheumatic fever has been suspected since 1635 when Ballonius <sup>1</sup> noted the occurrence of abdominal symptoms in rheumatism. Interest in this subject apparently waned for over 100 years and it was not until 1752 that Huxham <sup>2</sup> described the abdominal symptoms which precede or accompany rheumatic fever. In the past 15 years the condition has been noted and reported more frequently <sup>3</sup>.

An accurate estimation of the incidence of abdominal symptoms in rheumatic fever is not available because of a complexity of circumstances. Many of the abdominal symptoms are transitory and are deemed secondary to fever or to the salicylate therapy which is so widely used in this disease. Even when such patients are subjected to operation, the difficulty of differential diagnosis between rheumatic peritonitis and peritonitis of usual type, an acute surgical abdomen, persists. Since there is no typical microscopic rheumatic lesion in the peritoneum, even the pathologist examining appendices which have been removed at such operations, or examining blocks of peritoneal tissue removed at autopsy may fail to recognize the true etiological factor. Rhea <sup>4</sup> suggests that careful analysis of tissues from many locations in the peritoneum at necropsy of individuals dying from acute severe rheumatic fever will frequently show the presence of rheumatic peritonitis.

The gross and microscopic pathologic lesions of this condition have been studied by several investigators. Felson <sup>5</sup> has noted actual ileal lesions in an individual dying from rheumatic fever. These were ulcers that penetrated from the mucosa to the peritoneum. This finding suggests that some of the abdominal symptoms noted in rheumatic fever may have been due to lesions within the intestinal wall as well as on its peritoneal surface. Diffuse hemorrhagic changes have been described by Colleyes <sup>6</sup> in the intestinal wall.

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of patients with rheumatic fever. Friedberg and Gross<sup>7</sup> noted abdominal symptoms in active rheumatic heart disease. On later study, these proved to have been caused by periarteritis nodosa. The authors conclude that there is a close relationship between mesenteric periarteritis nodosa and rheumatic vascular disease. In a later communication Felson<sup>8</sup> suggests that the lymphoid tissue of the intestinal tract tends to "drain out the infectious agents in many diseases and thereby causes abdominal pathology and symptoms to appear." Aschoff-like bodies have been described by Paul<sup>9</sup> in sections of the diaphragm and from various other parts of the upper abdominal peritoneum. His patient had few striking abdominal signs or symptoms in life. Perihepatitis was noted at autopsy in fatal cases of rheumatic fever by Lenoble and Pineau,<sup>10</sup> Poynton,<sup>11</sup> Libman,<sup>12</sup> and Pierson.<sup>13</sup> However, necropsy studies do not give a true index of the frequency of this condition, for positive findings are not noted on postmortem examinations except in those instances in which the individual succumbs to an acute attack of rheumatic fever while the abdominal symptoms are present. Since this combination of events rarely occurs, Rally's<sup>14</sup> report of 140 cases of serositis in 3,500 autopsies of individuals dying of rheumatic fever does not offer an accurate picture of the actual incidence of this condition.

The present study is largely a clinical one and was undertaken after the observation of four patients whose presenting symptoms were abdominal in character and who, consequently, offered a problem in diagnosis.

The abdominal symptoms of rheumatic fever have been divided by Baraldi<sup>15</sup> into three groups. First the digestive, second the pseudo-appendiceal, and third, the peritoneal. It is to be emphasized that these symptoms may precede, occur concomitantly with, or follow other manifestations of rheumatic fever. It is even possible that abdominal infection may be the only evidence of an attack of rheumatic fever. This hypothesis may partially serve to explain the origin of those cases of rheumatic heart disease in which a history of articular, choreic, or other more frequently recognized manifestations of rheumatic fever can not be elicited. The greatest diagnostic problem occurs in those instances in which the peritoneal symptoms precede the development of joint or cardiac disease. In such cases the patient may present a series of signs and symptoms which are almost indistinguishable from those caused by acute inflammatory abdominal conditions, particularly acute appendicitis. The difficulties involved might best be illustrated by the case reports.

#### CASE REPORTS

On examination he was acutely ill and greatly distressed. The entire abdomen was tender and rigid. The rebound phenomenon was present. Urine was normal. Blood count showed 13,200 leukocytes, 76 per cent of which were polymorphonuclear and 13 per cent of these were immature forms. The red blood count was 3,620,000, the hemoglobin 98 grams. A diagnosis of peritonitis, probably secondary to acute appendicitis, was made. At laparotomy (at 9 p.m.) the entire peritoneum was edematous and injected. The smaller blood vessels on the peritoneal surface of the mesentery and the intestine were clearly visible. The appendicular peritoneal surface was involved but, not more severely than the adjacent ileum or parietal peritoneum. There was no free pus in the abdomen. The spleen and liver were both rather large and soft. The appendix was removed and the postoperative diagnosis was 'hematogenous peritonitis,' organism to be investigated. Pending the identification of the offending organism in the peritoneum, chemotherapy in the form of sulfathiazole was instituted empirically. During the first 24 hours, 12 grams (180 grains) were administered rectally. On subsequent days 6 grams (90 grains) were administered daily by mouth. The concentration of sulfathiazole in the blood was not determined. Under this régime the temperature dropped gradually to 98.6° F on July 16. The sulfathiazole was discontinued on July 17 and the patient was discharged on July 23 as recovered.

The pathological report of his appendix is as follows: "The organ is 9 centimeters in length, the serosal surface is smooth, and the vessels of the serosa are injected. The lumen is patent. On microscopic study, the mucous membrane is intact. There are many dilated capillaries filled with blood. There are many lymphocytes and polymorphonuclear leukocytes in the subperitoneal area."

It is interesting that the child had been under constant surveillance since infancy yet never had any cardiac murmurs or evidence of rheumatic disease of the heart joints, or tendons manifested themselves. He was a rather 'nervous' child, but, as this was a familial trait it is doubtful whether he ever had had chorea. The tonsils had been removed four years previously.

The culture taken from the abdomen yielded no growth and during his stay at the hospital, despite persistent search, no focus was found which may have excited the peritonitis. It was assumed, therefore, that the origin of his condition was probably pharyngogenic. On July 24, the day after his discharge, the original symptoms reappeared with abdominal pain and fever reaching 103.2° F (39.6° C). He was nauseated and vomited on two occasions. General examination again revealed only abdominal signs: general tenderness, retraction of the abdomen and rigidity. Sulfathiazole therapy was reinstituted and 6 grams (90 grains) were administered daily. The drug was continued for five days, during which period the temperature curve was not influenced at all. It was then discontinued since it was felt that the drug, if it were to be effective at all, should have caused some change in the condition after this period of time. Secondly, the drug itself may have been the cause of the continued pyrexia. Only on July 28 did the true nature of this disease begin to disclose itself with the appearance of several tender and painful nodules on the extensor surfaces of both legs and about the right elbow. These lesions may have been toxic manifestations of sulfathiazole therapy, or they may have been rheumatic nodules. However, when swelling, pain, redness and heat developed in the right ankle on July 31, followed by a similar condition in the left knee three days later, it seemed that the disease could safely be diagnosed rheumatic fever. Sodium salicylate, 4 grams (60 grains) per day, was administered with 0.6 gram (10 grains) of sodium bicarbonate on August 3 and daily thereafter. Although the left shoulder became inflamed on August 6, symptoms all disappeared by August 8. The temperature dropped rapidly in two days to 99° F (37.2° C) and continued between 98° F



(36.6° C) and 100° F (37.7° C) until August 17. The abdominal symptoms disappeared after one day of this therapeutic régime. A systolic murmur was first heard at the apex on August 5 and again on August 8 but was not heard again. Sedimentation rate on August 3 was 45 mm in one hour. This became normal on October 1 when the child was finally permitted out of bed. There were no residual signs or symptoms. That sulfathiazole intoxication did not cause the joint manifestations, nodules and fever was indicated the following spring when the child developed lobar pneumonia. He was treated with full doses of this drug and recovered rapidly with no allergic phenomena.

*Case 2* E DeF, age 10, female, was admitted to the hospital on February 26 1942, with a history of severe abdominal pain associated with nausea, vomiting and fever. The pyrexia had appeared four days earlier. The parent believed the condition to be a "cold in the stomach" and had treated her at home with hot applications to the abdomen, hot drinks by mouth, ice to the head and hot mustard foot baths. During this period the condition became worse until she finally sought medical advice.

The family history in this case was interesting and, as the author has taken care of this family for the past seven years, he was able personally to verify some of the unusual features. The father had always been well and had no cardiac symptoms. The mother lost both her parents at an early age, under 40. Both died suddenly while apparently in good health. The maternal grandparents had eight children. Five of these died suddenly while apparently in good health. The writer had examined several of these patients prior to their death, and the entire family lived in constant dread of sudden exitus. Two of those examined before death were entirely normal on clinical, radiographic and cardiographic study. The mother, however, had rheumatic heart disease, Class I-A. There was no cardiac disease in the patient's siblings (two sisters and one brother).

The past history of this patient revealed an attack of acute catarrhal jaundice two years before. There were no other pertinent past illnesses.

On examination the temperature was 102.2° F (39° C), the pulse 120, respirations 20. She was acutely ill. The legs were drawn up. The abdomen was retracted and very tender. Rigidity was present throughout. A systolic murmur was present at the apex, which had not been present two years previously on the last examination. The blood count showed white blood cells 9,200, 84 per cent polymorphonuclears, of which 12 per cent were immature. The urine was clear. Red blood count was 3,800,000 with 8.5 grams of hemoglobin. The differential diagnosis lay between rheumatic peritonitis, suggested by her familial cardiac history, and an acute purulent peritonitis. Since operation was believed to be premature even if this were a diffuse purulent peritonitis because of the need of awaiting localization, laparotomy was deferred. During the period of observation, supportive therapy was instituted to retard therapeutic differentiation. Hereafter 1 gram (60 grains) of sodium chloride and 1 gram (15 grains) of sodium bicarbonate were given daily. On February 27 there was much less abdominal pain. Tenderness and rigidity had

*Case 3* R S, age 10, male, was admitted to the hospital April 9, 1942, complaining of pain in the abdomen. On April 2 he had had a sore throat, with a temperature of 101.6° F (38.6° C). Sulfathiazole was given prior to admission, but the amount is not known. On April 5 large hives appeared on the skin of the abdomen and extremities and on April 6 pain appeared in the abdomen. There was no nausea and no vomiting, but anorexia was marked. The past and family histories were inconsequential.

On examination he was acutely ill. The respirations were not labored. The temperature was 102.2° F (39° C), pulse 120, respirations 28. The abdomen was splinted during respiration. A macular rash was noted on the arms and trunk. The lips were dry, the tongue coated and leathery. The heart was normal. The lungs were clear. The abdomen was rigid in the upper half and slightly looser in the lower half, particularly in the appendicular area. Clinical diagnosis was peritonitis of undetermined origin, probably not related to appendicitis. The urine was normal. The white blood count was 10,400, 86 per cent polymorphonuclear cells, of which 14 per cent were immature. There were 98 grams hemoglobin and the red blood count was 4,250,000. The Wassermann reaction was negative, sedimentation rate 160 millimeters in one hour (Westergren). Stool culture was negative. Agglutination tests for typhoid, paratyphoid and typhus were all negative. Consultation with the surgical staff was held, and it was felt that the child was too acutely ill to permit surgical intervention. It was deemed wiser to await localization. On the possibility that this might be rheumatic peritonitis, salicylate therapy was instituted at once and on April 10, 1942 the abdomen was much softer. The child seemed less seriously ill, although he was somewhat confused. The dosage was 4 grams (60 grains) per day with sodium bicarbonate 1 gram (15 grains), and on April 11 the temperature reached 99° F (37.2° C) at which level it remained for several days. On April 18 a systolic murmur was heard over the apex and transmitted to the axilla and a localized pericardial friction rub was heard at the apex. The abdomen was no longer retracted or tender. Roentgenographic examination on admission showed no cardiac or pulmonary abnormality. The electrocardiogram on April 27 was suggestive of pericardial change because of elevation of the ST segments in all standard leads. This elevation persisted on two subsequent studies at one month intervals. At this time, April 28, a diastolic murmur was first heard at the mitral area. The pericardial friction rub was heard for only two days. The temperature was normal on April 29, and a roentgenogram at this time revealed some straightening of the left cardiac border. Despite continued salicylate therapy, the temperature rose on May 2 to 100.4° F (38° C) and persisted in this neighborhood until his discharge on July 10, 1942. The sedimentation rate during the entire hospital stay continued high. On April 28 it was 69 millimeters, on May 30 it was 73 mm. On June 27 it was 73 mm in one hour. During this admission a diastolic aortic murmur was never heard, but the diastolic pressure dropped steadily, reaching a level of 35 mm of mercury on June 15. He was discharged at the request of his parents. He continued to receive salicylates while at home.

The patient was readmitted to the hospital on January 2, 1943. At this time he had all of the peripheral vascular phenomena of aortic insufficiency and a diastolic aortic murmur could easily be distinguished. The cardiac silhouette had increased in size and the general condition was considerably worse than on the first admission. The child was again taken home on January 21 in care of his family who were very cooperative and administered excellent convalescent care. Low grade fever persisted throughout the admission in January and continued as well at home. The cardiogram during the second admission revealed a prolongation of the PR interval to 26 seconds. Blood cultures taken both in the hospital and at home were sterile. Fluoroscopy on January 20, 1943, showed marked enlargement of the left auricle and

the left ventricle. While at home he continued in poor condition and died on February 12, 1943 in congestive failure. Autopsy was not permitted.

*Case 4.* V. M., age 37, female, was first examined on April 15, 1942. She complained of severe abdominal pain, fever and nausea.

Past history included a biopsy of a mass in the breast in 1938 which proved to be a fibroma and one normal pregnancy in January, 1942. There were no unusual postpartum sequelae. Aside from ulcerative colitis in her mother, the family history was not significant. There were no siblings. Her husband was living and well.

The patient complained of abdominal pain which started three days prior to examination as a vague discomfort in the umbilical area which gradually spread throughout the abdomen. She was moderately nauseated, but did not vomit until April 15, 1942, just prior to examination. The temperature had not been taken until April 14 when it was 101° F (38.2° C).

Examination revealed an acutely ill female, temperature 103.6° F (39.7° C), pulse 144, respirations 22. The legs were drawn up and the abdomen retracted. The abdomen did not move during respiration. General examination was negative except for the abdomen which showed marked rigidity and great tenderness throughout. The heart was normal and had been normal on many examinations during the past eight years. Laboratory studies revealed red blood cells 3,210,000, hemoglobin 7.8 grams, white blood cells 10,200, polymorphonuclears 76 per cent of which 12 were immature. Urine was normal. It was assumed that this patient had generalized peritonitis from some unknown cause and since it seemed wise to await the localization of symptoms before attempting any surgical intervention, she was treated empirically with sulfadiazine 2 grams (30 grains) immediately and 1 gram (15 grains) every four hours. Morphine was given for relief of abdominal pain. The temperature gradually dropped to 102° F in three days and remained there despite sulfadiazine levels of 18 milligrams per cent for four additional days. The abdomen was still tender throughout, but the rigidity was less marked. The patient did not look so alarmingly ill. However, since the temperature was not septic in type and localizing signs could not be found, it did not seem that an intra-abdominal abscess was developing. Sulfadiazine was stopped and salicylate therapy was instituted on April 22, 6 grams (90 grains), per day with sodium bicarbonate. The temperature dropped

## DISCUSSION

This investigation is purely clinical, as there is no laboratory proof of the diagnosis in any of these cases. However, several facts do stand critical examination,

1 The abdominal signs and symptoms subsided during the administration of salicylates and bicarbonate in large doses and did not respond to chemotherapy with the sulfonamides

2 In each case subjective and objective abdominal disease preceded either definite clinically recognizable acute rheumatic fever, rheumatic heart disease or subacute bacterial endocarditis

3 No patient had had rheumatic fever or rheumatic heart disease prior to the onset of the seizure described. One patient had a significant cardiovascular family history

4 A generalized peritoneal inflammation was observed clinically in the one case subjected to laparotomy. This case developed typical acute rheumatic fever later

5 In Case 4, the abdominal symptoms may have been embolic manifestations of subacute bacterial endocarditis appearing in a previously damaged heart. Several facts are against this possibility. This young woman never showed any signs of rheumatic or congenital heart disease. She had never had any subjective or objective cardiac abnormality on any of the previous examinations by several physicians. On her two hospital admissions, she was examined by the resident physician and by the anesthetist and no record of cardiac abnormality was noted on either chart. She believed firmly in regular physical examinations and the records over eight years show no pre-existing cardiac disease. She had been fluoroscoped on several of these examinations and the cardiac silhouette was recorded as normal. She had weathered her first pregnancy at the age of 37, just three months before the onset of symptoms, with no evidence of vascular difficulty. During her prenatal period she was examined regularly by an obstetrician who found no cardiac disease. No embolic phenomena appeared anywhere in her body during the period of abdominal complaints. Again, these facts fail to prove that she did not have preëxisting subclinical cardiac disease, but they do weigh against that assumption.

## CONCLUSIONS

1 Generalized peritonitis may be rheumatic in origin

2 In instances of abdominal disease in which clinical study points toward the diagnosis of diffuse peritonitis, the treatment of choice is usually conservative and non-operative. A therapeutic test in the form of large doses of salicylates with bicarbonate may be safely attempted in such cases to aid in the diagnosis of this disease. Such patients, however, must not exhibit a septic temperature, a mass in some abdominal area, or tenderness or rebound tenderness constantly referred to one area such as McBurney's point

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# CASE REPORTS

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## THE SYNDROME OF PRECOCIOUS PUBERTY, FIBROCYSTIC BONE DISEASE AND PIGMENTATION OF THE SKIN ELEVEN YEARS' OBSERVATION OF A CASE \*

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In 1922 Weil<sup>1</sup> first described the syndrome of precocious puberty, fibrocystic bone disease and pigmentation of the skin. Since then there have been reports of some 18 cases<sup>2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14</sup>. These are presented in table 1. Although the syndrome is interesting because it is uncommon and bizarre, its chief appeal arises from attempts to explain the various phenomena in the light of present day knowledge of neuro-endocrine mechanisms.

The patient to be presented has been under constant medical scrutiny since the onset of symptoms at the age of three, and has been under the author's care for 11 years.

### CASE REPORT

The patient is a 19 year old young lady who first came under observation at the age of eight.

The history revealed that she was the second born child and that her delivery was attended by considerable trauma to the mother.

The child developed well in the first three years. The only illness which occurred during this time was chicken pox. At the age of three however, vaginal bleeding suddenly appeared, this recurred at irregular intervals during the fourth and fifth years, gradually tapering off. At seven years of age it recurred, and since then has been a constant feature. In character the vaginal bleeding exhibited periods of metrorrhagia and amenorrhea, but during the last two years has tended to be fairly regular. Breast tenderness was present with the onset of the menses at age three, and at the age of four prominence of the breasts was first noted. At the age of five pubic hair appeared and asymmetry of the face became apparent.

When the patient was six years old, she sustained a fracture of the left humerus and in the roentgenograms taken at this time abnormalities of the bones were first brought to light.

Some time between the onset of the menses and the fracture of the humerus a small area of pigmentation appeared over the left lumbosacral region.

When the patient was nine years of age she was studied in the consultation service of Mt Sinai Hospital in New York, where the essential findings were as follows. Asymmetry of the face in the region of the right maxilla and the right eye, marked breast development, pubic hair and peculiar gait. Roentgen-ray studies revealed multiple areas of bone absorption in the left upper and lower extremities and

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The opinions and assertions contained herein are those of the writer and are not to be construed as official or reflecting the views of the Navy Department or of the Naval Service at large.

left ilium. The right side of the skull revealed bone condensation at the base and about the right orbit. A biopsy taken from the left humerus revealed fibrous osteitis. Calcium and phosphorus determinations were within normal limits. At this time also she was seen by Dr. Robert T. Frank, who had seen her previously at the age of seven. He made the observation that the vulva and internal organs were small and infantile for a patient who had been menstruating since the age of three. Studies of sex hormone in the urine revealed an increase in the amount which is found in children of her age.

TABLE I

Year	Author	Age of Patient	Precocity	Skeletal Changes	Pigmentation	Remarks
1922	Weil	9	Menstruation since infancy	Spontaneous fracture 18 mos	Abnormally pigmented skin	Sclerae blue
1932	Gaupp	8	3 yrs breast development, pubic hair, menstruation	2 yrs limp, 3-5 yrs fractures	Not stated	Bones showed osteitis fibrosa, normal parathyroids, $\frac{1}{3}$ removed
		9	9 yrs menses, breast, genital development	2 yrs rickets, 6 yrs bow legs, fractures	Pigmented mole	Neck explored, no parathyroid tissue identified
	Freedman	14 mos	4 mos menses, genital development	3 yrs fracture	6 mos brown pigmented areas	Laparotomy for adrenal tumor none found, small ovarian cyst
1933	Stalman	8	9 mos menses	5 yrs osteitis fibrosa-fractures	Birth-pigmented patches of skin	
	Snapper and Parisel	10	7 yrs menses	7-9 yrs fractures	Brown nevi	Surgical exploration neck, no parathyroid tumors found
1934	Goldhamer	9	2 yrs menses	3 yrs tumor jaw, 5 yrs fracture	Nevi	
1936-1937	McCune and Bruch	10	2 yrs menses, breasts, hair developed	1 yr bowing of legs, $3\frac{1}{2}$ yrs fractures	2 yrs brown patches in skin	Neck explored, no parathyroid tumors found, bone showed osteitis fibrosa
	Albright Butler Hampton Smith	23	7 yrs menses	8 yrs fractures	Brown spots	
		39	1 yr menses	10 yrs. fracture	Brown spots	
		8	$3\frac{1}{2}$ yrs menses	Seen in x-rays	Brown patches	Bone biopsy osteitis fibrosa

TABLE I—*Continued*

Year	Author	Age of Patient	Precocity	Skeletal Changes	Pigmentation	Remarks
1938	Mondor Ducroquet Leger Laurence	14	7 yrs menses	7 yrs fractures	Since birth	
1939 Jan	Summerfeldt and Brown	10	3 yrs menses, 5 yrs breasts and pubic hair	3 yrs waddling gait, bone cysts 6 yrs fractures	12 mos	Dense skull bones No parathyroid tumor found
		6	2 yrs menses, 6 yrs breasts and pubic hair	2 yrs limp, osteoporosis, fracture at 6 yrs	4 mos	Thickened base of skull
1939 Feb	Robson and Todd	33	Breasts, pubic hair at 6 yrs, menses at 7 yrs	7 yrs limp, fractures	At 33	At 4 grew unusually, at 33 neck explored no parathyroid tumor found
1939 Sept	F Braid	2½	2½ yrs menses	1½ yrs fractures, bones abnormal	3 mos	
1940	Diez	18	5 yrs menses, breasts and genital development	5 yrs limp, fractures		At 10 biopsy of bone, parathyroids explored, negative findings
1944	Dockerty, Meyerding and Wallace	35	7 yrs menses	7 yrs limp, 34 yrs fracture	At birth	Bone biopsy osteitis fibrosa, ovarian cyst

The conclusions reached at this time were that the patient had a "complicated endocrine disease, involving the parathyroid, suprarenal cortex and ovarian-pituitary functions. The disturbance in parathyroid function is evident from the marked rarefaction of the long bones and the tendency to fracture. It is not contraindicated by the finding of a normal blood calcium and phosphorus. It is supported by the microscopic study of the bone which is reported as showing evidence of an osteitis fibrosa. The pituitary, suprarenal cortex, ovarian syndrome is suggested by the precocious development of the breasts, pubic hair and onset of menstruation at age three. An intravenous pyelogram failed to reveal any evidence to support the possibility of a tumor of the adrenal cortex."

From this time on the patient developed nicely, increasing in height and weight until the age of 12 when she reached her maximum height (This was subsequently discovered to be due to early closure of the epiphyses).

At the age of 10, the patient began to suffer with vernal conjunctivitis and hay fever which were ameliorated by pollen injections.

Her menstrual periods continued in irregular fashion for some time and were characterized by long intervals, followed by periods of metrorrhagia. At the age of 12 the patient was given a course of injections with antuitrin-S, the purpose of which was to stimulate maturation of ovarian follicles and thus establish more



regularity Following this course of treatment the menstrual cycle was much more normal

At the age of fifteen the patient sustained a fracture of the left radius, following a fall The interesting features of this condition were that the fracture line was very fine, it ran through a cystic bone area, there was no displacement, but the pain was remarkably intense,—out of all proportion to the physical or roentgenographic findings

Intellectually the patient has developed most satisfactorily, her scholastic attainments being of the highest order In her relations with older people she impressed one as being quite mature

At the present time the patient is completing her second year in college studies,



FIG 1 The patient in 1937, 12 years of age Note the asymmetry of the face due to a bulge in the right frontal bone, and the right maxilla The right eye is lower than the left Compare with figure 3, a postero-anterior roentgenogram of the skull

always having achieved top ranking in her classes She is active and vivacious, and her general appearance, outside of the mild limp and asymmetry of the face, gives no clue to the profound changes which have taken place and to the long history of these changes

*Physical Examination* Physical examination at the present time shows a well developed, well nourished girl, 61 5 inches tall and weighing 110 pounds There is an asymmetry of the face due to a marked prominence of the right frontal and maxillary bones The right eyeball is lower than the left (figure 1) There is obstruction in the right nostril due to deviation of the septum (to the right) with a projecting spur making contact with the right inferior turbinate bone The middle turbinate shows cystic degeneration The dentition is normal and the prominence of the right maxilla is seen above the right upper teeth The thyroid isthmus is palpable

the heart, lungs and abdomen show no abnormalities. The breasts are prominent. The genital organs appear to be about normal in size and a normal female escutcheon is present. The left upper and lower extremities are thinner than the right. There is a lumbar scoliosis to the left with a tilt of the pelvis and an apparent shortening of the left lower extremity. There is an area of yellowish brown pigmentation about 4 cm in diameter in the skin overlying the left lumbosacral joint.

**Laboratory Findings** Laboratory studies have been done over the past 10 years and are summarized herewith.

#### I Blood

(a) Count (1934) Hemoglobin 12 gm, red blood cells 5.5 million, white blood cells 8200, of which 51 per cent were polynuclear leukocytes, 48 per cent were lymphocytes and 1 per cent eosinophiles.

(1936) Hemoglobin 10.5 gm, red blood cells 5 million, white blood cells 6800 with 34 per cent polynuclear leukocytes, 56 per cent lymphocytes, 7 per cent monocytes and 3 per cent eosinophiles.

(b) Sedimentation rate (1934) normal

(c) Kalin test (1934) negative

(d) Cholesterol (1934) total 230 mg per 100 cc

(1934) 215 mg per 100 cc

(1936) 152 mg per 100 cc

(e) Calcium (1934) 10.8 and 11.2 mg per 100 cc

(1936) 12.7 mg per 100 cc

(1942) 12.3 mg per 100 cc

(f) Phosphorus (1934) 5.0 and 4.7 mg per 100 cc

(1936) 3.6 mg per 100 cc

(1942) 3.5 mg per 100 cc

(g) Phosphatase (1942) normal

(h) Hamilton test (1942) negative

#### II Urine

(1934) }  
(1936) } within normal limits  
(1942) }

#### III Basal metabolic rate

(1934) minus 9

(1937) minus 4

IV Bone histology (reported by Dr Paul Klempner, Mt Sinai Hospital) (figure 2) Microscopic sections of one fragment of bone revealed bone trabeculae of unusual breadth and a conspicuous fibrillar structure. Between these bone trabeculae there is a cellular connective tissue apparently substituting the normal bone marrow. This tissue shows a uniform formation by fibroblasts and does not reveal any granulomatous areas. Sporadic osteoclasts are seen. In a second fragment the greater portion of the section was formed by a dense connective tissue within which metaplastic bone formation was seen. The microscopic findings are those of fibrous osteitis.

V Roentgen findings The roentgenographic findings in the skeleton are striking. In the skull (figures 3 and 4) areas of bone condensation are seen in the right frontal and maxillary areas with reduction in size of the right orbit. The lateral view shows marked condensation of the base in the anterior and middle fossae areas. Figure 5 shows areas of marked bone absorption in the left humerus and scapula, the epiphyses in the proximal ends of the humeri are almost completely closed. The bone biopsy seen in figure 2 was taken from the left humerus. Figures 6, 7 and 8 show areas

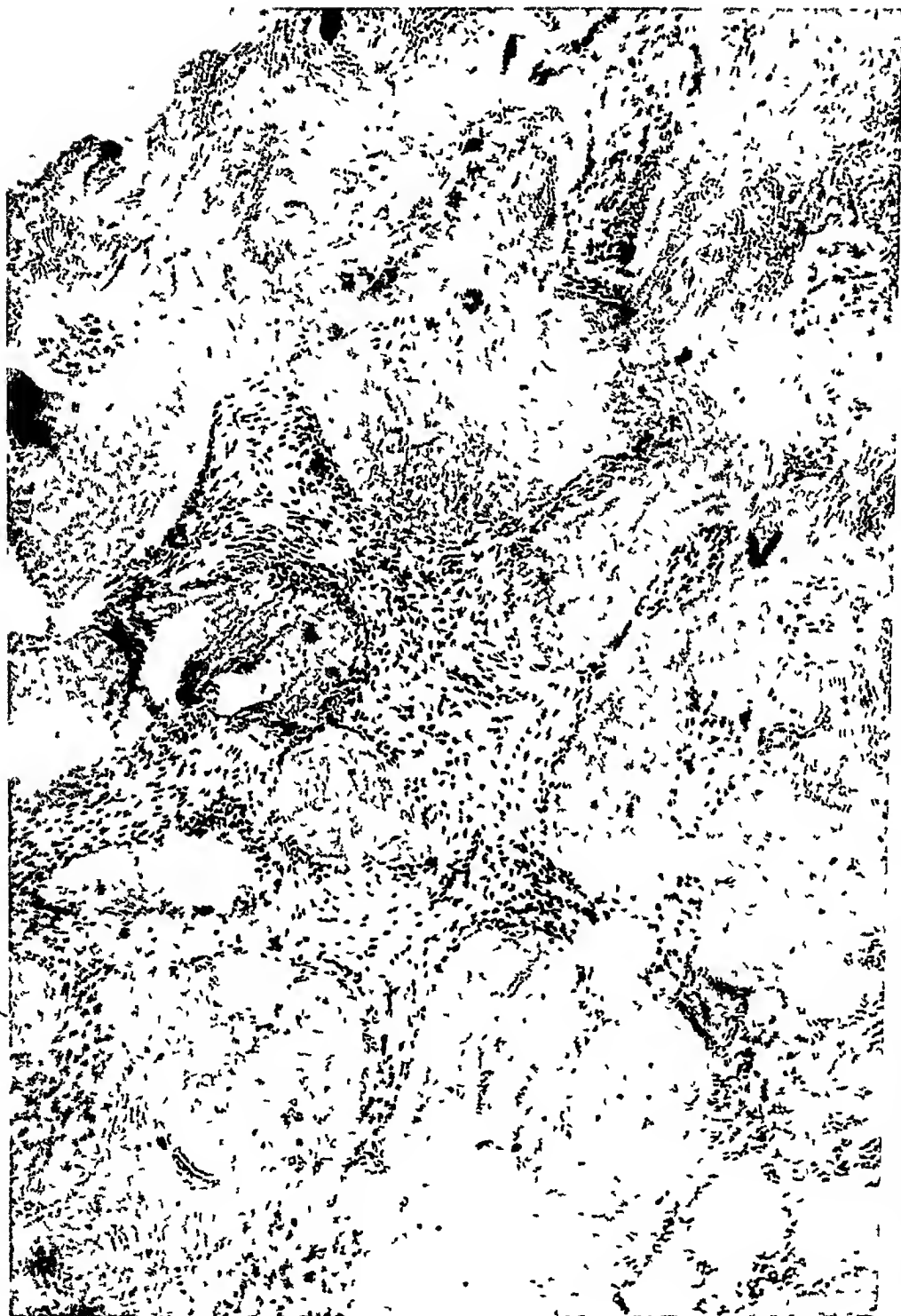


Fig 2 Section of bone from the left humerus, at the site of the fracture when the patient was 6 years old, specimen taken in 1934 at Mt Sinai Hospital, New York, shows thickening of bony trabeculae and replacement of marrow by fibrous tissue (Courtesy Dr Paul Klemperer, Mt. Sinai Hospital, New York)

of bone absorption in the left forearm, left pelvis, left femur and left tibia. In addition the closure of the epiphyses is well seen.

The roentgenograms reproduced were taken in 1937 when the patient was 12 years of age. The characteristics were (1) Involvement of right side of skull and left side of torso and extremities, (2) bone condensation in skull and bone absorption in trunk and extremities, (3) early maturation of skeleton.

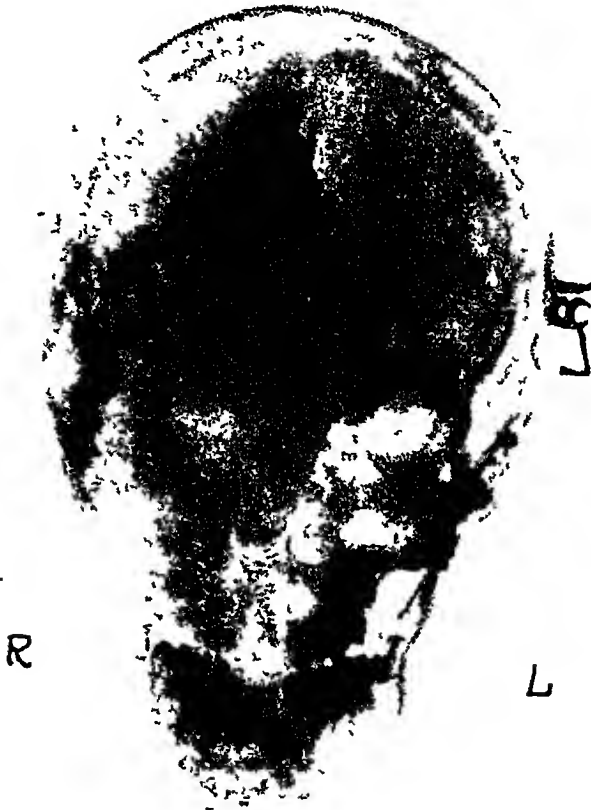


FIG 3 Postero-anterior view of skull showing density of bones on the right side and narrowing of right orbit. (An idea of the density of the bone may be obtained from the fact that in 1935 an attempt was made to give the patient more room in the right nasal fossa; only a few small pieces could be removed, and in doing so the operator broke his instrument.)

#### SUMMARY OF FINDINGS

Thus, it is seen that our patient presents the cardinal symptoms of an endocrine syndrome characterized by precocious puberty, fibrocystic bone changes and pigmentation of the skin.

The syndrome has been compatible in our patient with an otherwise normal life and development. The externally visible features have been slight asymmetry of the face, a mild hump and short stature—growth having stopped at the age of twelve when our patient reached her maximum height of 61.5 inches.

Laboratory studies revealed an increase in the amount of sex hormone in the urine for the age at which it was studied (nine years). Blood chemical studies have



FIG 4 Lateral view of the skull showing density of the bone at the base, the sella turcica shows no abnormalities

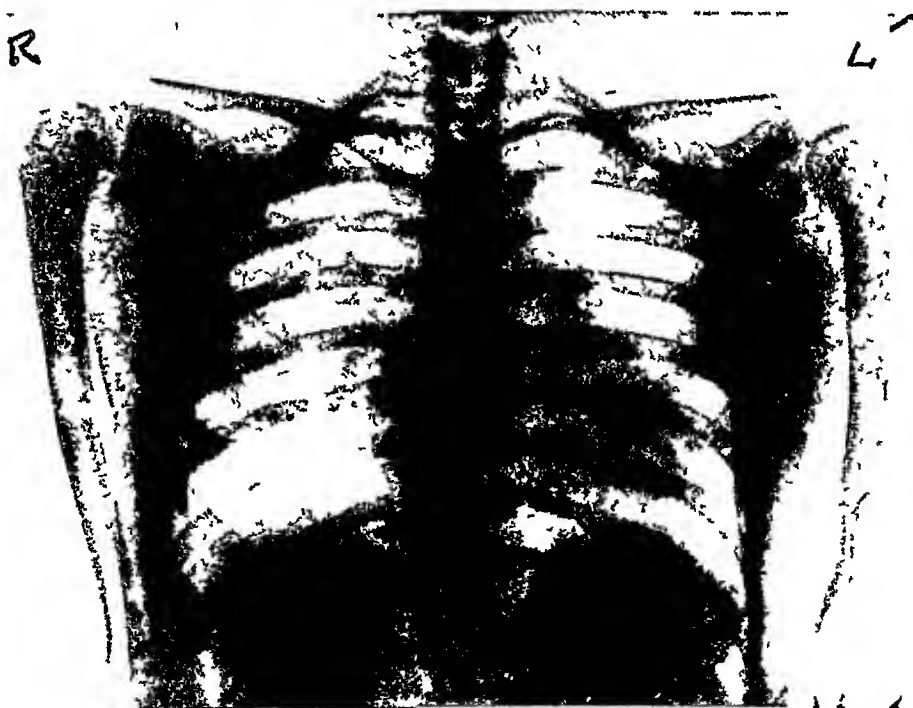


FIG 5 Showing areas of bone absorption in the left humerus and left scapula. The epiphyses are closed. The bone biopsy shown in figure 2 was taken from the left humerus

been within normal limits. Roentgenographic studies have shown profound and widespread changes, with slight progression of the findings in 10 years.

The only factor of possible significance in the patient's history is that her birth was extremely difficult, occasioning considerable trauma to the mother. This could conceivably have caused some damage to the central nervous system which became apparent in the unfolding of the patient's clinical condition.

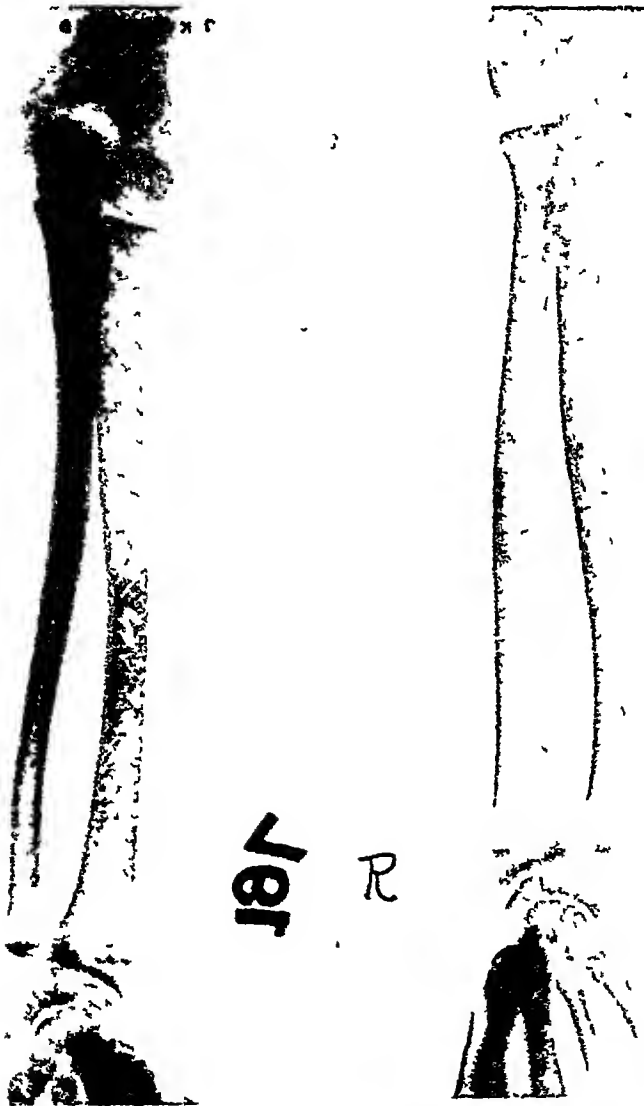


FIG 6 Showing areas of bone absorption in left radius, the epiphyses are closed

#### DISCUSSION OF THE SYNDROME

The remarkable skeletal changes which have been described in this syndrome have served to focus most of the attention on this feature, for this reason the early reports of these cases have been found under various titles indicating the skeletal changes.

However, careful analysis of the facts in the 19 cases thus far presented (including author's case) reveals that in only two instances were the skeletal changes first to appear. The precocious puberty was the presenting feature in 12, and skin pigmentation was first in five. In view of these facts, it would seem to be more fruitful to limit discussion of this syndrome to those cases showing precocious puberty and bone changes, and not to include the males who *do not* show any evidence of *precocity*, in fact, the reports of cases in males do



FIG 7 Showing areas of bone absorption in left ilium, left pubic bone and left femur. The neck of the left femur is thick and coarse, the inferior surface appears to be splintered.

not show early maturation of the skeleton as do the females, even though the roentgen lesions of the bones have the same gross appearance.

In the syndrome under discussion surgical explorations for parathyroid, ovarian and adrenal lesions have been negative. Autopsies have been few and incomplete, but a very exhaustive one, that by Sternberg and Joseph<sup>10</sup> on the case reported earlier by McCune and Bruch, failed likewise to supply an anatomic basis for the clinical picture. Since structural changes which might elucidate the clinical picture have not been demonstrated in any of these cases, we must turn to physiologic mechanisms for an explanation of the profound changes noted.

In considering these physiologic mechanisms attention must be directed to the

fact that although endocrine syndromes may be definitely patterned, e g , Graves' disease, Simmonds' disease, etc , many will show curious admixtures of features of various types depending on the particular variable which may be involved

Until definite experimental or clinical proof or both is available for all conditions, the explanation of many clinical pictures will remain in doubt However, recent developments in neuroendocrine physiology offer tempting paths for exploration and the author feels that in the syndrome under discussion some contribution to the analysis of the clinical condition can be made

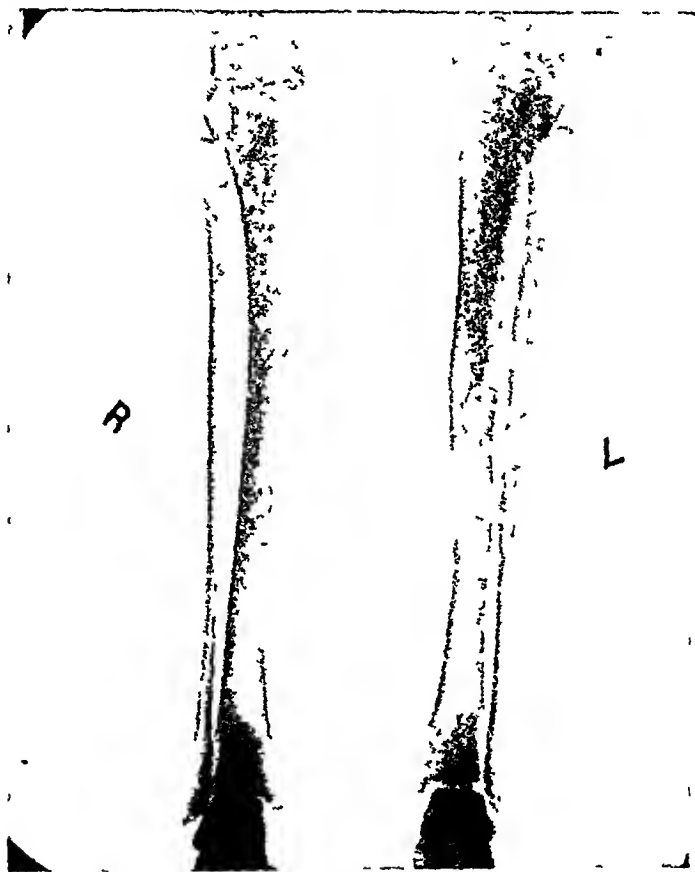


FIG 8 Showing areas of bone absorption in left tibia The epiphyses are closed

#### PRECOCIOUS PUBERTY

That a central mechanism, rather than a peripheral one, may be responsible for precocious sexual development is granted by many authors, e g , Novak,<sup>17</sup> Weinberger and Grant,<sup>18</sup> Sternberg and Joseph,<sup>19</sup> and Bing, Globus and Simon.<sup>20</sup> In fact, Novak, in commenting on the syndrome under discussion, suggests that the precocious puberty of this group is of the "cerebral type" The other authors just mentioned consider the hypothalamus the particular area responsible

It is generally accepted now that the "anterior lobe of the pituitary is the master gland of the endocrine system"<sup>22</sup> The hypophysis itself is controlled by nervous



as well as other glandular factors. Normally something occurs about the time of puberty which releases the pituitary from its inhibiting factors, and the activity of the gland is now seen in the remarkable growth of the body and the development of sex characteristics. In the opinions of Weinberger and Grant<sup>18</sup> and Bing et al<sup>19</sup> the factor of release resides in the hypothalamus. Smith and Dortzbach<sup>20</sup> have demonstrated the presence in the pituitary gland of gonad stimulating hormones even in the fetus. From these facts it may be reasonably deduced that a premature release of the restraining influence over the hypophysis could result in precocious puberty. What initiates the early release of these hormones cannot always be precisely indicated, but cranial injuries, intracranial tumors and encephalitis have been noted as precursors in cases of this type.<sup>18,19,21</sup>

In the author's case it is suggested that some injury might have occurred at birth which affected the hypothalamic region sufficiently to disturb the normal hypothalamic control over the hypophysis.

#### SKELETAL CHANGES

The skeletal changes are striking, and indeed, in many cases, have completely dominated the clinical picture because of their distribution and results (deformities and fractures). The question to be answered next is the relationship of the skeletal changes to the *pubertas praecox*.

Bremer<sup>22</sup> has suggested a plausible mechanism which fits in well with our concepts. "From a series of experiments on rats the following possibilities may be inferred. The general disease (i.e., *osteitis fibrosa cystica*) may be caused by a long continued excess of estrogen, probably acting through the parathyroid glands." That there is an excess of estrogen in the cases under discussion is evident by the precocious puberty which is so important a feature of this syndrome. That the bone lesions are specifically due to parathyroid activity seems to be most likely in view of the fact that it is the only known physiologic process which can mobilize calcium from the bones.

However, even if one were to insist on further evidence before accepting the foregoing, there are numerous instances of the association of hyperparathyroidism and pituitary diseases. Parathyroid tumors and bone disease have been reported frequently in acromegaly and in pituitary basophilism.

That the other features of hyperparathyroidism, such as hypercalcemia and negative calcium balance are not seen in these cases merely indicates that the process has been a slow one and the daily changes in blood chemistry so small that detection is not easy. It has been estimated quantitatively<sup>15</sup> that the normal skeleton contains about 900 grams of calcium, 3 to 6 grams could be lost per month without evidence either in blood chemistry or roentgenograms. However, after a long time, the latter might show osteoporosis or bone cysts—the results of calcium loss—without any detectable changes in blood chemistry. Also, when bone cysts or osteoporosis are present the process may have stopped and all that is visible is the end result.

Objection has been raised to the hormonal explanation of the bone disease on the ground that the lesions are frequently unilateral and not diffuse. This objection can be countered by many instances of asymmetrical or unilateral lesions in endocrine disease. Sternberg and Joseph<sup>10</sup> cite numerous examples such as unilateral exophthalmos in exophthalmic goiter, unilateral acromegaly

(also reported by Lichtwitz<sup>11</sup>), unilateral hemihypertrophy and hemiobesity, unilateral gynecomastia with cortical adrenal and testicular tumors, patchy and asymmetric changes in the bones in renal rickets have been described. It is recognized that the action of a hormone depends not only on its presence but also on local tissue susceptibility to the action of the hormone. Perhaps in the cases under discussion there is some underlying neurologic lesion which determines the variation in tissue response.

### PIGMENTATION

Little is known of the mechanism which produces this feature and the author leaves the elucidation of this symptom to future investigations.

### CONCLUSION

An additional case is presented, exhibiting the triad of symptoms

- 1 Precocious puberty
- 2 Fibrocystic bone changes
- 3 Pigmentation of the skin

The pathologic physiology is discussed and the hypothesis is advanced that the syndrome results from a hypothalamic (pituitary) parathyroid disturbance.

### ACKNOWLEDGMENTS

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### INFECTIOUS MONONUCLEOSIS A CASE FOLLOWING A SKIN ABRASION ON THE RIGHT LEG, AND INVOLVING ONLY THE RIGHT INGUINAL LYMPH NODES<sup>1</sup>

By NORMAN LARUE ANDERSON, M D, *Black Mountain, N C*, and  
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THE following case report is presented not only because it is, we believe, the first reported case of infectious mononucleosis following a known skin lesion, but also because it may offer additional evidence concerning the nature of the disease

#### CASE REPORT

The patient was a 27 year old white male physician living in a rural community. On September 14, 1942, he noted a small, slightly tender indurated area on the skin covering the lower internal aspect of the right tibia. This area was surrounded by an

<sup>1</sup> Received for publication April 3, 1943

ecchymotic zone measuring about 4 cm in diameter. The patient did not remember the cause of this lesion and considered it to be an insect bite at first.

On September 17 the patient became aware of moderate enlargement of the right inguinal lymph nodes where considerable tenderness also was apparent. On September 19 he began having a daily fever ranging from 99.6 to 101° F. The pulse rate averaged around 90 beats a minute. One of the right inguinal nodes enlarged to about 2 cm in length and 1 cm in width, the tenderness having increased. The patient went to bed on September 20, 1942, suffering from general malaise, weakness, neuralgic aches in most of the joints, a severe right parietal headache, and a mild erythematous macular rash over the back and buttocks which occurred on the fourteenth day after the onset. The fever and soreness of the right inguinal lymph nodes persisted for about 25 days. No other lymph nodes except the right inguinal ones were ever involved during the course of the disease, and the spleen was never palpable or tender. Both cold and hot compresses applied to the area gave questionable relief from discomfort.

Consecutive blood counts and smears done from the onset of fever exhibited a typical picture of infectious mononucleosis with the mononuclear cells reaching a maximum of 73 per cent of the total leukocytes on October 8. Leukopenia was characteristic at the onset with a total of 3,300 leukocytes on September 23. The sedimentation rate (Cutler), normally 2 mm in one hour for the patient, was 5 mm in one hour on September 23, and 3 mm in one hour on October 5. Urine and stool analyses were negative. The patient made a prolonged but uneventful recovery, feeling normal again in six weeks' time. The primary lesion on the leg healed and the right inguinal lymph nodes regressed to normal size. The blood picture also returned to normal as evidenced by a blood count on October 30 (see table for consecutive blood counts).

TABLE I\*

Date	Time	Hgb	RBC	WBC	PMN	Juv	Lymph	Mono	Eos
3-26		90%	4.3	6,100	69%		28%	2%	1%
†9-23	10 a m	90%	4.3	3,300	50%		46%	4%	
9-25	10 a m			4,500	28%	(7%)	48%	21%	3%
9-27	4 p m			8,400	25%	(2%)	65%	8%	2%
9-29	4 p m			9,200	25%	(3%)	69%	4%	2%
10-1	4 p m			8,200	38%		58%	4%	
10-3	10 a m			9,400	34%	(2%)	57%	8%	1%
10-5	10 a m			7,600	31%		64%	4%	1%
10-8	11 a m			7,400	26%		71%	2%	1%
10-13	11 a m	82%	4.1	5,200	30%		64%	5%	1%
10-17	11 a m			4,700	40%		54%	5%	1%
10-22	11 a m			5,200	46%		46%	8%	
10-24	5 p m	90%	4.9	7,600					
10-30	4 p m			6,400	56%		32%	8%	4%

\* Compilation of the blood counts was made with the technical assistance of Miss Cornelia Varner.

† Onset of infectious mononucleosis.

Heterophile antibody agglutinations with sheep cells done on blood serum at the Piedmont Hospital in Atlanta according to the method of Paul and Bunnell<sup>1</sup> were positive. On October 2 there was positive agglutination at 1:128 dilution, and on October 8 the positive titer had decreased to 1:64. Since the serum specimens were mailed unrefrigerated a distance of 70 miles before testing it is possible that the antibody titers were considerably higher at the bedside. According to Kracke and Garver<sup>2</sup> a positive agglutination in a dilution of 1:64 is considered diagnostic in the absence of serum sickness, whereas Straus and Bernstein<sup>3</sup> consider a dilution

of 1:512 as diagnostic, although they occasionally make the diagnosis of infectious mononucleosis in cases not showing a positive agglutination at any titer. There was no history of serum sickness in the patient, and the same test, done 18 months previously, had been negative. As indicated by Straus and Bernstein, a falling titer at weekly intervals is much more significant than single determinations.

Representative blood smears were sent to Dr. Roy R. Kracke of the Department of Pathology at Emory University and he reported as follows. "The smears show a predominance of lymphocytic cells exhibiting a considerable variation in morphology, some being large, others small, some showing vacuolated cytoplasm, others showing dark, intensely stained blue cytoplasm. A few have the appearance of monocytes. This pleomorphic picture, including these various cell types, is quite characteristic of infectious mononucleosis, and I feel quite certain that this is the disease involved, particularly considering the lymphadenopathy. I would expect the heterophile antibody test to be positive."

### DISCUSSION

The etiology of infectious mononucleosis has yet to be established definitely. In 1929 Nyfeldt<sup>4</sup> produced the typical blood picture of infectious mononucleosis in rabbits by exposing them to *Bacterium monocytogenes*. Later, in 1929, Gorham, Smith and Hunt<sup>5</sup> also produced the typical blood picture in guinea pigs by inoculating them with the membrane from the pharynx of a young girl who had Vincent's angina.

Later evidence, however, indicates that the etiological agent is a virus. Nettleship<sup>6</sup> in 1942 succeeded in producing an ectodermal proliferation and monocytic cell infiltration in the chorio-allantoic membrane of chick embryos by inoculating the embryos with sterile Berkefeld filtrates of nasal washings and blood obtained from cases of human infectious mononucleosis. No inclusion bodies were found, but a suspension of similarly treated ground chick membranes when injected into rabbits caused a monocytosis, but failed to produce a significant heterophile antibody response.

Recently Bornstein<sup>7</sup> demonstrated, in an interesting case of severe cystitis, a positive heterophile antibody reaction of the serum. A strain of *Escherichia coli* was cultured from the blood of this case, and this culture contained heterophile antigen. The antibodies could be differentiated from those observed in serum sickness and in infectious mononucleosis, and were of Forssman's type.

In the case reported it seems possible that the infecting agent, instead of taking the usually considered route through the upper respiratory system and causing pharyngitis with regional lymph node involvement, was probably introduced through an abrasion on the right leg causing a regional involvement of the right inguinal nodes only, but producing the typical systemic symptoms and blood picture of infectious mononucleosis, along with positive heterophile agglutination tests. Since the patient regarded his initial lesion as an insect bite, could this mean that perhaps infectious mononucleosis might be transmitted through an insect vector as well as through the usually considered respiratory route?

### SUMMARY AND CONCLUSIONS

1. A typical case of infectious mononucleosis following a skin abrasion on the right leg, and involving the lymph nodes only of the right inguinal region is presented. This is believed to be the first case of this nature reported.

2 It is thus evident that the infecting agent of infectious mononucleosis, whether it be bacterial, virus, or otherwise, may possibly gain access to the body by other than the almost exclusively reported respiratory route

3 It is interesting to note that, as in other local infectious processes, infectious mononucleosis is primarily a local process, causing predominant symptoms in the local lymph nodes draining the infected area, and causing the typical systemic symptoms regardless of the site of entry

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### A CASE OF TETRALOGY OF FALLOT WITH VERRUCOSE ENDOCARDITIS \*

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A MAJORITY of the cases of the cyanotic group of congenital cardiac anomalies present the combination known as the Tetralogy of Fallot

Most of these cases are encountered in infants and children, the mean age in Abbott's<sup>1</sup> series being 12 years of age White and Sprague<sup>2</sup> reported a case of Tetralogy of Fallot in which the patient lived to the age of 59 years and nine months This is the oldest proved case on record Fallot,<sup>3</sup> in his original article, reported a case which lived to 36 years of age Revilliod<sup>4</sup> also reported a case of the Tetralogy in a 36 year old female LaFitte's patient<sup>5</sup> died at the same age

More recently, Volin and Flaxman<sup>6</sup> reported the Tetralogy in a male who lived to 41 years of age In 1939, Herndon, Voss and Donovan<sup>7</sup> reported a case which lived to the age of 49 years

The case we are reporting is the seventh oldest proved case of the Tetralogy of Fallot on record Of particular interest is the heavy manual labor which the patient performed during his lifetime, despite the presence of a lesion which is supposedly incompatible with longevity or a useful physical activity

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It is generally supposed that death is caused by the development of bacterial endocarditis or else by pulmonary tuberculosis, and it was of the former condition that our patient died. However, in Abbott's series<sup>1</sup> of 51 cases, which is the largest reported, only one patient had a superimposed bacterial endocarditis. Fallot's<sup>3</sup> case also died of a terminal endocarditis. Pescatore, Wolffe, and Digilio<sup>8</sup> reported a case of Tetralogy of Fallot in a 20 year old male who died of a septic endocarditis. The remainder of the cases of Tetralogy of Fallot which have been reported died of causes not related to the cardiac defect. Therefore, it would seem that the occurrence of a bacterial endocarditis, on such a congenital cardiac defect as the Tetralogy of Fallot, is not so frequent a finding as we have been led to believe.

#### CASE REPORT

W H, a 32 year old, white male, was first admitted to the Cook County Hospital on January 9, 1941, with complaints of dyspnea, chills and fever of nine days' duration and precordial pain of four days' duration. He had a congenital cardiac lesion, having been cyanotic since birth. There was no history of any previous



LEAD I



LEAD II



LEAD III



LEAD IV

FIG 1 Electrocardiogram showing marked right axis deviation

attacks of cardiac decompensation, and the patient had been working as a truck driver up to the onset of his present illness. He had previously been dyspneic on strenuous exertion, but never sufficiently so to warrant his going to bed.

He had had scarlet fever at the age of 10 years, and an appendectomy at the age of 17 years. No history of rheumatic fever was obtained, although during childhood he suffered from frequent sore throats.

Physical examination at the time of admission revealed a well developed, well nourished, young male who was in moderate respiratory distress and was deeply cyanotic. His temperature was 98° F, his pulse 84 per minute, and respirations 24 per minute. The blood pressure was 92 mm Hg systolic and 68 mm diastolic. The



FIG 2 Postero-anterior view of chest showing evidence of right upper mediastinal widening and enlargement of right heart border

chest showed dullness to percussion at both bases with an absence of breath sounds and decreased tactile fremitus at the left base. The cardiac borders were five centimeters to the left of the sternum in the fifth interspace and one and one half centimeters to the right of the sternum. The cardiac rhythm was regular. Auscultation revealed a systolic murmur at the apex and also at the base. This murmur increased in intensity, to reach a maximum in the third left interspace where it was heard as a rumbling and blowing sound. The liver was palpable two centimeters below the right costal margin. No other abdominal masses were palpable. There was marked clubbing of the fingers and toes with an intense cyanosis of the nail bed. There was no peripheral edema.

The patient was placed on three grains of digitalis a day for one week, while



at complete bed rest. After this interval, as his dyspnea progressively diminished, he was allowed up. He was discharged nine days after admission.

He was seen in the Cardiac Clinic as an outpatient on January 28, 1941. Since his discharge from the hospital he had been taking a grain and a half of digitalis every day and limiting his activity. His condition was good, there being no evidence of cardiac decompensation.

Nothing further was heard from him until May 5, 1941, when he was readmitted to the hospital with complaints of pains in both feet and in his right arm and hand of one week's duration. On admission his temperature was  $100.4^{\circ}\text{F}$ , pulse rate 92



FIG 3 Left oblique view of chest showing aortic knob on right side

per minute, and respiratory rate 28 per minute. Examination of the chest and heart revealed findings essentially similar to those on the first admission. Of significance were the presence of petechiae in the conjunctiva of the right eye, extreme pain on pressure over the toes and the fingers of the right hand, and a firm, blue, elevated lesion one centimeter in diameter on the left palm. The spleen was not palpable.

The temperature, during his entire hospitalization, was elevated between  $99.6^{\circ}\text{F}$  and  $102^{\circ}\text{F}$ , reaching  $106^{\circ}\text{F}$  before death. Repeated blood cultures during this time were consistently negative. One week after admission the palmar lesion became fluctuant and was aspirated. A few drops of thick whitish blood-tinged fluid were obtained, direct smear of which showed an occasional chain of faintly staining cocci. Culture of the fluid showed small, gram positive cocci in pairs and in short chains.

Five grams of sodium sulfathiazole were given intravenously on May 13 and repeated on May 14. For two days thereafter sulfathiazole (2 gm every 4 hours) was given orally. At the end of this time a diffuse erythematous rash was noted, along with nausea and vomiting, and the drug was stopped. On May 21, sulfanilamide (1 gm every four hours) was started and continued to May 30. During the entire course of sulfanilamide therapy the temperature was not affected. He died on May 31, 1941, 26 days after his second admission.

**Laboratory Data.** Daily urine examinations at the time of his second admission consistently showed red blood cells, white blood cells, and granular casts. There was a slight elevation of the non-protein nitrogen, the values being as high as 54 mg per 100 cc. The blood Wassermann reaction was negative. There was a gradual



Fig 4 Left ventricle showing interventricular septal defect with aorta riding both right and left ventricle.

diminution in the hemoglobin and red blood cell count, from 132 per cent hemoglobin and 6.72 million red blood cells at the time of his first admission to 98 per cent hemoglobin and 5.0 million red blood cells, six days before patient died. During this time the white blood cell count rose from 8,300 cells per cubic millimeter to 24,600 cells per cubic millimeter shortly before death.

Electrocardiograms showed a marked right axis deviation (figure 1).

Roentgenographic examination of the chest revealed a fullness of the right upper mediastinal shadow (figure 2). The aortic knob could not be made out. On fluoroscopy the right mediastinal widening was seen to be due to the aortic arch and was well shown by a left oblique view (figure 3).

A clinical diagnosis of Tetralogy of Fallot with superimposed bacterial endocarditis was made.

Permission for necropsy limited to the heart only was obtained

Autopsy (performed by Dr William Shaeffer) The pericardial sac contained 60 c.c. of a clear yellow fluid The heart weighed 425 grams The myocardium was dark purple red and firm The left ventricle measured 15 millimeters in thickness and the right ventricle was 11 millimeters in thickness

The pulmonary artery was markedly stenosed, the mouth measuring 32 millimeters in circumference There were two large valves, one having a small septum partially



FIG 5 Right ventricle showing relative thickness of wall, mural thrombus located on tricuspid valve

dividing this leaf There was a slight fusion of the leaflets at the commissures Just below the pulmonary valve there were small bead-like projections, one millimeter in diameter, on the endocardium The intima of the pulmonary artery was smooth and shining

The right auricle and the right ventricle were markedly dilated The transverse diameter of the right ventricle was 16 centimeters and the vertical diameter was the same The tricuspid valve showed thickening of the free edge by atheromatous plaques On one of the leaflets of the tricuspid valve was a large, friable, purple red vegetation which measured 2.5 by 2 by 1.5 centimeters

The free edge of the mitral valve was thickened by atheromatous plaques. The chordae tendineae were thickened and fused.

The aorta measured 78 millimeters in circumference and its intima contained single fatty and hyaline plaques. Just below the aortic valve there was a defect in the interventricular septum which measured 2.5 centimeters in diameter. The right leaflet of the aortic valve was continuous with the endocardium of the right ventricle.

The left coronary artery was thin walled with a smooth intima. The right coronary artery had a double ostium. The wall was slightly thickened, the lumen was dilated, and the intima contained fatty and hyaline plaques.

The anatomic diagnosis was

- 1 Congenital cardiac deformity, with
  - a Interventricular septal defect
  - b Stenosis of the pulmonary artery
  - c Marked hypertrophy and dilatation of the right ventricle
  - d Bicuspid pulmonary valve
  - e Dextrorotation of the aorta
- 2 Verrucose vegetations of the tricuspid valve
- 3 Double ostium of the right coronary artery
- 4 Endocardial sclerosis
- 5 Slight fibroplastic deformity of the mitral valve

#### DISCUSSION

The criteria for the diagnosis of the Tetralogy of Fallot are essentially similar to those originally promulgated by Fallot<sup>3</sup> in 1888 and added to by McGinn and White in 1936. The diagnostic points include

- 1 Cyanosis which has been present since birth
- 2 Marked pulmonary osteoarthropathy
- 3 Polycythemia
- 4 The presence of a loud systolic murmur heard best at the pulmonic area

In the presence of these four clinical findings, the Tetralogy of Fallot may be suspected.

Confirmatory evidence may be obtained by roentgenogram. The widening of the right upper mediastinum and the absence of an aortic knob on the left (figures 2 and 3) are very suggestive of dextroposition of the aorta. On fluoroscopy, the right upper mediastinal widening may be identified as the pulsating aorta. The electrocardiogram shows a marked right axis deviation (figure 1).

Since the case which we presented conformed to most of these criteria, a clinical diagnosis of Tetralogy of Fallot was made. The febrile course, the presence of petechiae and the palmar lesion suggested the presence of a superimposed endocarditis. This diagnosis was made despite the consistently negative blood cultures. The postmortem findings confirmed the clinical impression.

#### SUMMARY

A case of Tetralogy of Fallot in a 32 year male who died of a bacterial endocarditis is presented. The diagnosis was made clinically and verified by post mortem examination. The salient features in the diagnosis of Tetralogy of Fallot are presented.

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## ANOTHER CASE OF INTESTINAL MYIASIS\*.

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WHEREAS larvae of *Gastrophilus* species which produce horse bots are true intestinal parasites, larvae of other genera (*Lucilia*, *Calliphora*, *Prophila*, *Fannia*, *Phormia*, *Musca*, etc) are apparently plastic enough in their habits to live for different periods of time in the digestive tract of mammals

The older opinion regarding the prevalence of intestinal myiasis is well expressed by Walsh who says, "Taking everything into consideration, we doubt whether, out of ten thousand cases, where the larvae of two-winged flies have existed in considerable numbers in the human intestines, more than one single case has been reported in print by competent entomological authority for the edification of the world" (Banks 1912) The accumulated data available at present indicate that many ingested fly larvae do not survive the environmental conditions of the digestive tract whereas others do The latter produce intestinal myiasis of different degrees of intensity

Precisely how fly larvae acquire entrance to the digestive tract is not clear Entrance is generally thought to occur by way of the mouth but it seems entirely possible and very probable that entrance may also be secured by way of the anus Herms and Gilbert (1933) say that it is easy to understand how larvae of the cheese fly (*Prophila casei*) might be ingested since they normally occur in foods such as cheese, bacon, ham, etc, but that this view is not plausibly tenable with reference to commonly reported infestations by larvae of the lesser house fly (*Fannia canicularis*) and the latrine fly (*F. scalaris*), whose food is principally fecal material These authors point out that these species under

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† Dr Marcus W Lyon, Jr, formerly of the South Bend Clinic, South Bend, Indiana died May 18, 1942 The junior author is a member of the Department of Biology, University of Notre Dame, Notre Dame, Indiana

stress of circumstances may be compelled to lay their eggs in decomposing vegetable matter or meat Neveu-Lemaire (1912) says that *Lucilia sericata* often lays its eggs on the thin skin of the rumps of sheep and after hatching, the larva penetrate and live in the tissues of the animal Chandler (1941) reported a case of urinary myiasis caused by a species of *Lucilia*, probably *L. sericata* Entrance in this case probably occurred by way of the vaginal orifice Riley and Johannsen (1938), however, suggested that larvae of *Psychoda albipennis* migrated from the rectum into the bladder of a child exhibiting urinary myiasis The present case involves larvae of *L. sericata* and an undetermined species of *Sarcophaga*

#### CASE REPORT

A 23 year old housewife (Mrs W B) living in an unscreened house in the residential part of South Bend, Indiana, consulted the South Bend Clinic on several occasions for various complaints In 1938 she complained of a burning sensation on urination At that time her appetite was good and her bowels were regular without the use of laxatives, but she occasionally became nauseated and vomited after eating In July 1940 her urinary condition became worse and necessitated her getting up at night Her doctor at that time said she had bladder trouble Physiological conditions present immediately prior to the onset of menstruation seemed to intensify the symptoms and her menstrual periods, otherwise normal, became painful especially during the first two or three days Nausea and vomiting became frequent Wassermann Kline, Mazzini, and pregnancy tests were negative, erythrocytes numbered 4 030,000 (with slight hypochromia), hemoglobin 10.44 gm per 100 cc, leukocytes 6,000 with an essentially normal differential count In December 1940, she consulted the clinic again, complaining of abdominal distress Examination revealed a possible cyst of the right ovary A hemorrhagic cyst about the size of a hen's egg was removed Recovery was uneventful and two months later she reported that her bladder condition was better

On July 5, 1941, the patient said that she thought she saw worms in her stools and submitted one (stool) for examination It was of normal color and consistency and negative except for a few threads (10-12 mm long) of definite plant origin On August 5, 1941 she submitted another stool of the same general nature except that it contained many large dipterous larvae (about 10 mm by  $1\frac{1}{2}$  mm in diameter) When the patient first reported the "worms" she had the opinion of her physician that they were ordinary pin worms and gentian violet had been prescribed and taken without effect This was one month before she submitted the stool containing the vegetable fibers The patient was of the opinion that she passed "worms" in her stools for a period of one month

For the sake of completeness the following additional information is given Weight 113 pounds (lost 9 lbs in summer of 1940), rather thin and poorly nourished pulse 124 and of good volume, blood pressure 130 mm Hg systolic and 60 mm diastolic, sedimentation rate normal, temperature normal, tongue and tonsils normal, sinuses normal, thyroid normal, lungs clear, a harsh systolic murmur present over apical region, liver and spleen impalpable, appendectomy (1930) scar well healed, patellar reflex active, pupils equal and regular, several teeth missing, one tooth carious No children Mother and father living and well, has two brothers and a sister Uses neither alcohol nor tobacco She complained of 'heart trouble' since 1932 At the time of the intensification of her urinary condition (July 1940) she was teaching school and drove 65 miles daily Her urine at the time was normal except for a high specific gravity (1.026) and a pH of 7.5

The present case, characterized by the symptoms of nausea, vomiting, and abdominal distress was conspicuous by the absence of diarrhea which is generally one of the chief symptoms of intestinal myiasis. The history regarding the urinary trouble is interesting since Chandler (1941) recorded a case of urinary myiasis with essentially the same symptoms, which suggests that the present case possibly manifested urinary complications. How the larvae entered the intestinal tract is not known. Extracorporeal contamination of the feces seems remote and was ruled out entirely in the case reported by Herms and Gilbert (1933).

Most interesting perhaps is the tenacity of infestations of this sort. Although apparently of superior intelligence, this woman lived in an unscreened house and complained of a large number of flies. It is most unusual that an individual of this apparent type could knowingly or accidentally ingest large fly larvae sufficiently often to account for an infestation of a month's duration. The larvae were large enough to be readily noticeable as well as repugnant to a normal individual. If they were ingested when small enough to escape detection, it naturally follows that they developed considerably in the human digestive tract which, to say the least, seems very remarkable. This possibility however, is not untenable since Parker (1922) is of the opinion that *Calliphora erythrocephala* is not only capable of living in the digestive tract of man but actually reproducing in it paedogenetically. Herms and Gilbert (1933) state that the chances of reinfestation were supposedly nil during one year in an obstinate case of intestinal myiasis which was apparently of several years' standing.

The larvae in the present case were preserved when received by the senior author but were reported alive when passed by the patient. Living larvae of the cheese fly (*Prophila casei*) were recovered from a bloody human (child) stool in 1901 by Thebault, according to Riley and Johannsen (1938) and experimentally from a dog by Herms and Gilbert (1933). The last-named authors (1933) recovered living larvae of the genera *Calliphora*, *Sarcophaga*, and *Lucilia* from a human case of intestinal myiasis. Intestinal myiasis has also been reported for the larvae of *Fannia scalaris*, *F. canicularis*, *Musca crassirostris*, *Apiochaeta rufipes*, *Musca domestica*, *Eristalis tenax*, *Sarcophaga hemorroidalis*, *Hermetia illucens*, etc (Chandler 1940, Riley and Johannsen 1938).

The authors gratefully acknowledge the cooperation of Dr C A Bishop of South Bend, Indiana, for acquisition of the larvae and of Professors W B Herms and M A Stewart, both of the University of California, for identification of the organisms.

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## EDITORIAL

### *TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS*

SUBACUTE bacterial endocarditis has long aroused the keen interest of physicians, an interest which is perhaps a little out of proportion to the frequency of its occurrence as compared with many other infections. This is doubtless due in part to the highly variable and often bizarre clinical symptoms which it presents, although certain of these are so characteristic that the diagnosis should be suspected if not positively made in a large majority of the cases if the observer is alert to the possibility of its occurrence. Interest is also stimulated by the course of the disease which, in spite of its frequently apparent mildness, relatively slow course and occasional remissions, proceeds inexorably to a fatal termination in most cases in spite of any type of treatment which hitherto has been available. The fact that arrest or apparent recovery occurs in rare instances (about 1 per cent of the cases) has served largely to tantalize those interested in other victims of the disease and to arouse false hopes as to the efficacy of some therapeutic procedure which happened to be under trial at the time.

The introduction of the sulfonamides and more recently of penicillin naturally led to a trial of these drugs in subacute bacterial endocarditis. Although the results thus far reported have been disappointing, they are, nevertheless, somewhat more favorable than those obtained by older methods of treatment. Among others, Kelson, White and their associates have made a particularly careful study of this problem, and we are fortunate in being able to present in this number of the *Annals of Internal Medicine* reports of their most recent investigations.

As these investigators clearly point out, the problems involved in the treatment of subacute bacterial endocarditis differ notably from those encountered in the case of most other infections. Although this disease may be caused by several different species of bacteria, in a large majority (about 95 per cent) of the cases some nonhemolyzing type of streptococcus is involved. These streptococci usually have little or no virulence for laboratory animals. In man they normally lead a saprophytic existence in the mouth and throat, they show little or no tendency to invade the tissues, and although they frequently enter the blood stream in small numbers, they are quickly eliminated by the normal defensive forces unless they find unusual conditions especially favorable for their development.

As is widely known, these conditions are found largely in heart valves (or mural endocardium) which have been injured, usually by rheumatic fever, or which are congenitally defective. In the thrombi which form in such areas, the streptococci find conditions favorable for their development, in that they have abundant nourishment and are protected mechanically from phagocytosis and probably to some extent at least from the anti-



bodies (and possibly from antibacterial drugs) which are usually abundant in the plasma. It appears to be the inaccessibility of the organisms rather than any inherent virulence on their part which makes possible their continued development and thus brings about the progressive course and unfavorable outcome of the infection. Indeed, endocarditis is the only human disease which has been proved to be caused by these organisms.

Kelson and White have analyzed the factors which appear to restrict the effective action of the sulfonamides in this disease. They stress particularly the readiness with which the streptococci acquire resistance to the sulfonamides, although the organisms as a rule are initially sensitive to these drugs. Resistance is especially apt to develop if a previous course of sulfonamide has been given which was inadequate either in dosage or duration, or if treatment is interrupted because of drug intoxication and resumption is attempted later. Resistance appears sooner or later, however, during the first uninterrupted course of treatment, and these observers have found that organisms which have acquired resistance to sulfapyridine, the most potent sulfonamide in this infection, are resistant to the others also.

They also point out that the sulfonamides exert a bacteriostatic rather than bactericidal action on the organisms, and elimination of the latter depends upon the natural defensive forces of the body, particularly phagocytosis. The action of the latter is largely blocked by the location of the organisms within the thrombi.

To offer a reasonable hope of being effective, therefore, treatment must first make the organisms accessible to attack, and second, the drug must be given early, in adequate dose, and without interruption because of symptoms of drug intoxication, unless the latter are so severe as to be an immediate and grave risk to life. The first requisite they attempt to secure by the administration of heparin in dose sufficient to slow coagulation and thus presumably to limit the development and enlargement of the thrombi while the antibacterial agent is being administered. In addition to two cases previously published,<sup>1</sup> the authors report 10 additional recoveries in a series of 34 cases treated by this method. These results, although they still leave much to be desired, are substantially better than those which have been obtained with sulfonamides alone.

Other observers have not obtained such favorable results with these measures.<sup>2</sup> Katz and Elek,<sup>3</sup> for example, even feel that the use of heparin should be abandoned. As Kelson has pointed out, however, in many of these unsuccessful cases the treatment was not properly administered. There is rarely any observation as to the susceptibility of the strain of streptococcus to the drug. In many cases sulfonamides have been given in interrupted

<sup>1</sup> Kelson, S. R., and White, P. D. A new method of treatment of subacute bacterial endocarditis, *Jr Am Med Assoc*, 1939, **cxiii**, 1700.

<sup>2</sup> Lichtman, S. S. Treatment of subacute bacterial endocarditis: current results, *Ann Int Med*, 1943, **xix**, 787-794.

<sup>3</sup> Katz, L. N., and Elek, S. R. Combined heparin and chemotherapy in subacute bacterial endocarditis, *Jr Am Med Assoc*, 1944, **cxiv**, 149-152.

courses, a procedure which frequently results in the development of drug fastness. Frequently, too, heparin was not administered simultaneously with the sulfonamide. There is general agreement that heparin alone is ineffective. Serious objections have been advanced to the use of heparin because of the danger of inducing hemorrhage, particularly cerebral hemorrhage. A substantial number of such accidents have been reported.<sup>3</sup> Kelson himself reports this complication in three of 40 cases during treatment, but he claims that deaths due to cerebral accidents were not more frequent in patients so treated than they had been before the use of heparin was inaugurated. The data now available are not sufficient to establish how great this risk really is. However, if further experience shows that a recovery rate of 30 per cent or better can be maintained, one would be justified in incurring a substantial risk of bleeding in a disease in which the outlook otherwise is so nearly hopeless.

There is good reason, also, to believe that the details of treatment can be improved. It may prove possible to simplify the technic by substituting dicoumarin orally administered for heparin by vein, although at present the activity of the former cannot be so precisely controlled. It is more likely that penicillin may supplement or replace the sulfonamides as an antibacterial agent. Penicillin is far less toxic than the sulfonamides, and it appears that the organisms are much less prone to become resistant to its effects. Although the permanent results thus far reported from the use of penicillin alone are not substantially better than those obtained with the sulfonamides,<sup>4</sup> Loewe et al.<sup>5</sup> have reported immediate favorable results with sterilization of the blood and clinical recovery in seven consecutive cases (six of which were streptococcal and one pneumococcal) treated with penicillin and heparin. These cases, however, had been observed only for short periods. One of the 10 cases reported by Kelson had received heparin and penicillin, supplemented toward the close of treatment by sulfadiazine.

On the basis of the data now available it is not possible to reach a definite conviction as to the efficacy of these measures, or as to what the best type of combined treatment may be. The favorable results reported by Kelson and White, and by Loewe, however, warrant further trial of these measures in clinics where large numbers of cases are available, and where the patients can be thoroughly studied and properly selected and the details of treatment adequately controlled. These procedures are still in the experimental stage, however, and until much more is known as to the results obtainable and the dangers involved, then promiscuous employment by those without experience is far more likely to do harm than good.

<sup>3</sup> KEEFER, C. S. Discussion, Jr. Am. Med. Assoc., 1944, cxxv, 636.

<sup>4</sup> LOEWE, L. R., et al. Combined penicillin and heparin therapy of subacute bacterial endocarditis, Jr. Am. Med. Assoc., 1944, cxxv, 144-149.

## REVIEWS

*Chemistry and Physiology of the Vitamins* By H. R. ROSENBERG, Sc D 674 pages, 23.5 × 16 cm Interscience Publishers, Inc., New York 1942 Price, \$12.00

The author has made an outstanding contribution to the vitamin literature by presenting a comprehensive monograph on the chemistry and physiology of the vitamins. The introductory chapter includes a definition of the vitamins which distinguishes this group of substances from hormones and from various constituents of foods. Realizing certain limitations inherent in the definition, the author has justified its use and has suggested two new terms for substances which do not conform to the definition in all respects. Those enzymes which contain vitamins would be called vitazymes and those substances which act as sources of energy or as building units in addition to their vitamin-like functions would be termed vitagens. The latter group, including the essential fatty acids, essential carbohydrates, choline and related compounds, are discussed briefly in the appendix.

The vitamins are discussed according to their alphabetical nomenclature. The known information about each is systematically presented. All the names under which the vitamin has been known are listed, together with a chronological outline of the various discoveries which led to their chemical characterization of the vitamin. The historical survey is followed by a section on occurrence and distribution. The chemistry is thoroughly covered and includes isolation, properties, chemical constitution and synthesis, industrial methods of preparation, biogenesis, and methods of determination. Many of the chemical reactions are presented in detail. The methods for the determination of the vitamins are divided into chemical, biological, and biochemical. They are evaluated as to their accuracy, specificity and to their use in the determination of deficiency states. Other reactions useful for the detection of hypovitaminosis are also given. Various units which are in common use are compared with the international unit when possible.

The physiology of microorganisms, plants, and animals is given. The animal physiology is subdivided into the metabolism of the vitamin, the physiological basis for its action, together with a short review of the pathological aspects of hypovitaminosis.

Following the sections devoted to the known vitamins, the author has discussed briefly a group of the non-identified vitamins. These are substances which appear to be essential for the growth and development of certain animals or for bacteria, but further study is necessary to prove whether or not they are separate entities.

The book includes a list of abstracts of vitamin patents issued in the United States of America, Great Britain, Germany and France. These are arranged in the same general order as the rest of the text. There is a complete author and subject index.

The systematic presentation of the material, together with the extensive bibliography, makes this volume of great value to anyone interested in the vitamin field.

M. A. A.

## BOOKS RECEIVED

Books received during November are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Saunders' System of Clinical Medicine* Twelfth Edition Edited by E. C. WARNER, M.D., F.R.C.P. 1168 pages, 22 × 15.5 cm 1944 Williams and Wilkins Company, Baltimore Price \$9.00

- Clinical Practice in Infectious Diseases* Second Edition By E H R HARRIES, MD Lond, FRCP, DPH, and M MITMAN, MD Lond, MRCP, DPH, DMRE With a foreword by W ALLEN DALEY, MD Lond, FRCP, DPH 570 pages, 22 × 15 cm 1944 E & S Livingstone, Edinburgh Price, \$6 00
- The Art of Resuscitation* By PALUEL J FLAGG, MD 453 pages, 23 5 × 16 cm 1944 Reinhold Publishing Corporation, New York City Price, \$5 00
- Arthritis and Allied Conditions* Third Edition By BERNARD I COMROE, A B, MD, FACP 1359 pages, 24 × 15 5 cm 1944 Lea & Febiger, Philadelphia Price, \$12 00
- Bacteriology for Medical Students and Practitioners* Third Edition By A D GARDNER, D M, FRCS 264 pages, 17 × 11 cm 1944 Oxford University Press, New York City Price, \$2 50
- An Outline of Tropical Medicine* By OTTO SAPHIR, MD 86 pages, 20 × 14 cm 1944 The Michael Reese Research Foundation, Chicago
- Sulphonamides in the Treatment of Meningococcal Meningitis* Report to the Scientific Advisory Committee (Department of Health for Scotland) 20 pages, 24 5 × 15 5 cm 1944 His Majesty's Stationery Office, Edinburgh Price, \$ 10
- Esclerose Valvulares Calcificadas Estudo Anátomo-Patológico, Radiológico e Clínico com Apresentação de cem Casos* By ROBERTO MENEZES DE OLIVEIRA, MD 154 pages, 23 × 16 cm 1944 Tipografia do Patronato, Rio de Janeiro
- Arquivos da Polícia Civil de São Paulo* Volume VI (2 ° Semestre)—1943, Volume VII (1 ° Semestre)—1944 468 pages (Vol VI)—550 pages (Vol VII), 28 × 19 cm 1943 and 1944 Tip do Gabinete de Investigações, São Paulo, Brasil

## COLLEGE NEWS NOTES

### NEW LIFE MEMBERS

The College is gratified to announce that the following Fellows of the College became Life Members during the month of December

Dr Rudolph H Sundberg, San Diego, Calif  
Dr Frank J Holioyd, Princeton, W Va  
Dr John H Keating, New York, N Y

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### A C P MEMBERS IN THE ARMED FORCES

Dr Robert H Siver (Associate), Cockeysville, Md, has entered upon active service as Captain, (MC), AUS, bringing the number of College members on active military duty to 1720

The following members of the College have been honorably discharged from active duty

Dr Ellery G Allen (Major, MC, AUS), Syracuse, N Y  
Dr A Carlton Ernstene (Lt Colonel, MC, USNR), Cleveland, Ohio

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### GIFTS TO THE COLLEGE LIBRARY

#### *Books*

Dr William Nimeh, F A C P, Mexico, D F—"Almamar de la Medicina Arabe"  
Dr F M Pottenger, F A C P, Monrovia, Calif—"Symptoms of Visceral Disease," sixth edition  
Dr James J Waring, F A C P, Denver, Colo—"Quartercentenary of the Publication of Scientific Anatomy, 1543-1943" This book is dedicated to Dr Waring and is No 92 of a limited edition personally signed by the author, Nolie Mumey

#### *Reprints*

Dr Benjamin M Bernstein, F A C P, Brooklyn, N Y—1 reprint  
Daniel B Faust, F A C P, Colonel, (MC), AUS—1 reprint  
Jack D Kirshbaum, (Associate), Lieutenant Colonel, (MC), AUS—1 reprint  
Dr Louis Bonner Owens, F A C P, Cincinnati, Ohio—1 reprint  
Frank B Queen, F A C P, Lieutenant Colonel, (MC), AUS—1 reprint  
James J Waring, F A C P, Denver, Colo—4 reprints and a mimeographed monograph by the National Research Council, Division of Medical Sciences on, "Spontaneous Pneumothorax"

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### A C P REGIONAL MEETING AT CHAPEL HILL, N C

A Regional Meeting of the College for the state of North Carolina was held at Chapel Hill November 3, 1944, under the general chairmanship of Dr Paul F Whitaker, F A C P Governor for North Carolina. The Program Committee consisted of Dr William B Dewar, F A C P Chairman, Dr W Reece Berryhill, F A C P, and Dr Thomas W Baker, F A C P. The program was conducted in the auditorium of the University of North Carolina School of Medicine. Presentations included "Recent Advances in the Treatment of Cardiovascular Diseases," Dr Ed-

ward S Orgain (Associate), Durham, "The Value of X-Ray Examination as an Aid to the Diagnosis of Curable Heart Disease," Dr James P Rousseau, F A C P, Winston-Salem, "Ageing," Dr William DeB MacNider, F A C P, Chapel Hill, "Sarcoidosis," Dr Paul P McCain, F A C P, Sanatorium, "A Consideration of Meckel's Diverticulum," Dr Donnell B Cobb, Goldsboro, "Chronic Non-calculous Cholecystitis," Dr Claiborne T Smith, F A C P, Rocky Mount In the evening a reception and dinner was given at the Carolina Inn, addressed by Dr Whitaker, the Governor About 100 physicians attended the meeting, of whom 60 (75% of the North Carolina members not on active military duty) were present

The North Carolina state meeting of the College next year will be held at Duke University Medical School, Durham Dr James P Rousseau, F A C P, Dr Edward S Orgain (Associate), and Dr E M Hedgpeth, F A C P, constitute the new program committee

#### A C P REGIONAL MEETING AT PHILADELPHIA

The 7th Annual Regional Meeting for Eastern Pennsylvania, New Jersey and Delaware was held at Philadelphia, December 15, 1944, in conjunction with the Postgraduate Course in Special Medicine, December 4-15, and the Annual Meetings of the Committees and Regents of the College The program has previously been published in these columns The scientific program, both morning and afternoon, was received with high acclaim The evening Dinner Meeting was addressed by President Ernest E Irons, Major-General George F Lull, Deputy Surgeon General, U S Army, Washington, D C, Brigadier General Charles R Glenn, Deputy Air Surgeon, U S Army, Washington, D C, and Captain Richard Kern, (MC), USNR, envoy of the Surgeon General of the U S Navy

The attendance from the Philadelphia area was extremely gratifying, since approximately 90% of local Fellows were present

	<i>Fellows</i>	<i>Associates</i>	<i>Guests</i>	<i>Total</i>
(MC), U S Army	11	4	55	70
(MC), U S Navy	2		30	32
(MC), U S Public Health Service		1	2	3
	13	5	87	105
Civilians	148	25	100	273
Total Registration	161	30	187	378

The Haffenreffer Fellowship has been established at Brown University for the encouragement of advanced study and research under the direction of the Department of Medical Sciences

It is open to graduates of approved medical schools, who have served an internship in an approved hospital, or who have had two or more years of practice Training beyond a year of internship is a desirable qualification Candidates for the fellowship must be persons of evident earnestness of purpose who have signified their intention of specializing in the field of internal medicine in practice research or teaching

The stipend is \$1,800 per year, the duration, one year with the expectation of a second year Further information and applications may be obtained from the Department of Medical Sciences, Brown University, Providence R I

### BARUCH FELLOWSHIPS IN PHYSICAL MEDICINE AT HARVARD

The Harvard Medical School announces Fellowships in Physical Medicine supported by grants from the Baruch Committee on Physical Medicine. The purpose of these fellowships is to provide a three year training for academic and clinical careers in the field of Physical Medicine. Fellowships are granted annually, but subject to renewal for a total duration of three years. The first year will be wholly or in part devoted to basic research related to Physical Medicine in one of the pre-clinical sciences such as physiology, anatomy or biophysics. The second year will be spent in clinical training in Physical Medicine at the Massachusetts General Hospital and other hospitals affiliated with the Harvard Medical School. In the third year fellows will be assistants in Physical Medicine with clinical responsibilities. For candidates with extensive previous training, one year clinical fellowships will also be granted.

Applicants must have an M.D. degree from an approved medical school and a minimum of one year internship in an approved hospital. The annual stipend will be \$2500 (single), \$3000 (married). Applications may be obtained from the Dean, Harvard Medical School, 25 Shattuck Street, Boston 15, Massachusetts.

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The American Dietetic Association will hold its 28th Annual Meeting at the Netherland-Plaza Hotel, Cincinnati, Ohio, October 15-19, 1945.

### DR. PAULLIN HONORED

Dr. James Edgar Paullin, F.A.C.P., was awarded the Certificate of Distinguished Achievement at appropriate exercises conducted by the Atlanta Chamber of Commerce at the Ansley Hotel, Atlanta, on Tuesday, November 21, 1944.

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Col. Edgar V. Allen, (MC), AUS, Consultant in Medicine to the Seventh Service Command, is currently the Chairman of the Section on Experimental Medicine and Therapeutics of the American Medical Association.

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Lt. Comdr. William L. Powers, (MC), USNR, (Associate), formerly of Wichita Falls, Texas, after twenty months in a hospital in the South Pacific, is now on duty with the U. S. Naval Hospital at Norman, Okla.

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Lt. Col. Charles M. Caravati, (MC), AUS, F.A.C.P., has been transferred from the Percy Jones General Hospital, Battle Creek, Mich. to the Woodrow Wilson General Hospital, Staunton, Va., where he is Chief of Medical Service.

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Dr. Carl R. Howson, F.A.C.P., has resigned as Medical Director of the La Vina Sanatorium and also as Medical Director of The Hastings Foundation for Tuberculosis Research of Pasadena, Calif., effective January 1, 1945, in order to devote himself entirely to private practice. The two positions are assumed on a full-time basis by Dr. Edward Kupka, F.A.C.P., recently Chief of the Bureau of Tuberculosis in the California Department of Public Health. The Hastings Foundation has purchased a plot of ground adjacent to the La Vina Sanatorium on which it is currently erecting the Charles Cook Hastings Home, which will house the research and sanatorium activities of the Foundation.

Dr Samuel M Feinberg, F A C P, associate professor of medicine, Northwestern University Medical School, addressed the Academy of Medicine of Toledo, Ohio, November 10, on "Molds in Allergy—a Decade of Progress in the Etiology of Respiratory Allergy"

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Lt Col J W H Rouse, (MC), AUS, (Associate), formerly of San Antonio, Texas, is now commanding the 60th General Hospital in the Pacific area

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Lt Comdr Harold J Harris, (MC), USNR, F A C P, addressed the Graduate Fortnight of the New York Academy of Medicine, October 19, 1944 on "Brucellosis—Special Problems in Diagnosis and Treatment" Comdr Harris addressed the Discussion Group of the Scientific Staff of The American Museum of Natural History on November 29, 1944 on "Animal Vectors in Brucella Infection"

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Dr Philip Reichert, F A C P, Secretary of the New York Cardiological Society, 480 Park Ave, New York City, announces that the Society has inaugurated a project to study the rôle of trauma in the causation of cardiac disabilities. The work is planned as a continuing series of investigations and reports, with subcommittees on clinical statistics, on experimental investigation, on pathology, and on the medico-legal aspects. The general objective of the entire research is to study all angles of relationship between trauma and heart disease and to formulate, on the basis of the widest investigation possible, a reasonable code for the guidance of expert opinion. Funds for the work will be provided out of the Society's treasury and by various grants. An introductory meeting will take place January 24 at the New York Academy of Medicine. All interested organizations, practicing physicians and officials are invited to participate.

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Col John Minor, (MC), AUS, F A C P, for nearly two years Chief of Medical Service at the Woodrow Wilson General Hospital, has been appointed Medical Consultant for the Third Service Command of the U S Army and is located at the Headquarters Third Service Command, Baltimore 2, Md

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Dr Edward L Turner, F A C P, for many years President of the Meharry Medical College, Nashville, Tenn, resigned that appointment on January 1, 1945, to enter private practice in internal medicine at Bradford, Pa

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#### MICHAEL REESE HOSPITAL OFFERS COURSE IN ELECTROCARDIOGRAPHIC INTERPRETATION

Dr Louis N Katz, F A C P, Director of Cardiovascular Research at the Michael Reese Hospital, Chicago, announces that he will direct a course in electrocardiographic interpretation at that hospital from February 14 through May 2, 1945, the course to consist of twelve lectures, one a week on each Wednesday from 7 00 to 9 00 p m. The course is offered primarily to general practitioners in the Chicago area. The sessions will deal with the interpretation of electrocardiograms, illustrated by lantern slides. Emphasis will be placed on chest leads and on the importance of the electrocardiogram in coronary sclerosis and myocardial infarction. The mechanism and interpretation of heart irregularities will be developed. The fee for the course is \$25.



Dr William G Leaman, Jr, F A C P, Philadelphia, addressed the Eastern Section Meeting of the American Federation for Clinical Research at the Massachusetts General Hospital, Boston, December 9, 1944, on "The Prolonged Use of Mercupurin in Congestive Cardiac Failure"

#### REPORT FROM THE OFFICE OF THE SURGEON GENERAL, U S ARMY

Col William C Menninger, (MC), AUS, F A C P, Chief Consultant in Neuropsychiatry, was the recipient of the first annual Lasker award in Mental Hygiene by the National Committee for Mental Hygiene at its New York annual meeting November 9. The award was given for "outstanding contribution to the mental health of the men and women of our Armed Forces"

#### Recent Promotions, Medical Corps Officers

##### Lieutenant Colonel to Colonel

Herman Lande, F A C P, New York, N Y  
 Frank Denette Adams, F A C P, Brookline, Mass  
 Neil Louis Crone, F A C P, Boston, Mass  
 Harold Foor Machlan, F A C P, Hines, Ill  
 Waldo Beattie Farnum, F A C P, Riverdale, N Y

##### Major to Lieutenant Colonel

Robert Collier Page, F A C P, Detroit, Mich  
 Kendall Adams Elsom, F A C P, Philadelphia, Pa  
 Robert J Needles, F A C P, St Petersburg, Fla  
 James Porter Baker, F A C P, Richmond, Va  
 Andrew DeJ Hart, Jr, F A C P, Charlottesville, Va  
 Frank Meyers, F A C P, Buffalo, N Y  
 Joseph Bank, F A C P, Phoenix, Ariz  
 James Lewis Blanton, F A C P, Fairmont, W Va  
 Ernest Marvin Tapp, (Associate), Walla Walla, Wash  
 Philip Walling Brown, F A C P, Rochester, Minn  
 Milton Henry Clifford, F A C P, Cambridge, Mass  
 Dickinson Sergeant Pepper, F A C P, Philadelphia, Pa  
 Abraham Max Balter, F A C P, Aspinwall, Pa  
 William Walton Bondurant, Jr, F A C P, San Antonio, Tex  
 Hermon Camp Gordiner, (Associate), Troy, N Y

Lt Col Phillip T Knies, F A C P, Army Quarantine Liaison Officer, is directing a new quarantine branch in the Epidemiology Division, Preventive Medicine Service. The new program, which aims to extend precautionary measures throughout the Army's far-flung routes of travel, is part of the Medical Department's continuing battle against disease, which has given this country the healthiest fighting forces in the world and the healthiest soldiers in any war in history.

Major General George F Lull, F A C P, Deputy Surgeon General, dedicated the Vaughan General Hospital at Hines, Ill, recently. This hospital will specialize in medicine and psychiatry. Col Victor C Vaughan, in whose memory the hospital has been named, was one of the leading bacteriologists and toxicologists of his day. He was commissioned a Major in the U S Army during the Spanish War and was a member of the Commission headed by Walter Reed to study the cause and prevention of typhoid fever, then epidemic in military camps. During the World War, Colonel Vaughan served in the Office of The Surgeon General and was on

the executive committee of the general medical board of the Council of National Defense. He served as President of the American Medical Association and of the American Tuberculosis Association. He was awarded the Distinguished Service Medal for his outstanding work in epidemiology and was made a knight of the Legion of Honor by the French government. He died in 1929.

The Upjohn Company, Kalamazoo, Mich. was presented with the Army-Navy Award for their production record in supplying vital pharmaceuticals for the Armed Forces. In a letter to the Company Major General George F. Lull, F.A.C.P., Deputy Surgeon General, said, "The men and women of your Company can well be proud of your production record. Your organization has given this office the greatest cooperation in the supplying of pharmaceuticals—the use of which is vital and necessary in performing the mission of the medical department. The products you supply to the Medical Department have been outstanding both in volume produced and quality of production."

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Brigadier General James S. Simmons, F.A.C.P., Chief of the Preventive Medicine Service, Surgeon General's Office, has been made President-Elect of the American Society of Tropical Medicine.

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Brigadier General Hugh J. Morgan, F.A.C.P., Chief Consultant in Medicine, addressed the National Post-War Venereal Disease Conference held recently (Nov. 9 and 10) in St. Louis, Mo., on the "Treatment of Gonorrhea and Syphilis in the U. S. Army."

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Dr. John Walker Moore, F.A.C.P., Louisville, Ky., has been made President-Elect of the Association of American Medical Colleges. Dr. William S. McEllroy, F.A.C.P., Pittsburgh, Pa., was elected Vice-President.

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Dr. Virgil P. Sydenstricker, F.A.C.P., Professor of Medicine, University of Georgia School of Medicine, Augusta, has been commissioned Colonel, and will serve with the United Nations Relief and Rehabilitation Administration, as Chief Counsel in Nutrition of Western Europe.

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Capt. Louis H. Roddis, (MC), USN, F.A.C.P., twice Editor of the Naval Medical Bulletin, will be responsible for the preparation of the Official Naval Medical History of the War. He will work at the Bureau of Medicine and Surgery, Washington.

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Dr. Henry B. Mulholland, F.A.C.P., Charlottesville, was inducted as President of the Medical Society of Virginia at its last annual meeting in October.

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Dr. William J. Bryan, F.A.C.P., Rockford, is now President of the Illinois Trudeau Society. Dr. David F. Loewen (Associate), Decatur, was chosen President-Elect.

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Dr. E. K. Shelton, F.A.C.P., Los Angeles, recently received the honorary degree of Doctor of Science from the University of Colorado School of Medicine, Denver, from which he graduated in 1911.

Dr Howard K Petry, F A C P, heretofore Medical Superintendent of the Harrisburg State Hospital, has recently been appointed Director of the Bureau of Mental Health of the Pennsylvania Department of Welfare

Dr Robin C Buerki, F A C P, Dean of the Graduate School of Medicine of the University of Pennsylvania, is now in Peru attending a hospital conference as a representative of the American Hospital Association

Major Donald R Feigunson, (MC), AUS, F A C P, is now Chief of Medical Service, Regional Hospital, Camp McClellan, Ala, this appointment having been made on October 4, 1944

Captain Gerald W Smith, (MC), USN, F A C P, formerly Commandant of the Philadelphia Naval Hospital, is now the Commandant of Fleet Hospital No 113, which was commissioned by the Navy on December 9 This hospital has a 2,000-bed capacity In four months the entire hospital has been constructed—255 fifty-foot steel buildings, including Surgical, Medical and Neuro-psychiatric Wards, administration buildings, post office, laundry, galley and mess halls, operating room, laboratories, x-ray and dental departments, corpsmen's and nurses' quarters, garage, and maintenance buildings

Colonel Robert E Thomas, (MC), USA, F A C P, Chief of the Hospitalization Division, United Kingdom Base, Communication Zone, European Theater of Operations, has been extended the honor of being elected a member of the Royal Society of Medicine of England

A War Time Graduate Medical Meeting devoted to Hematology was held Dec 7, 1944, at the Fletcher General Hospital, Cambridge, Ohio The following program was presented Greetings by Colonel Forrest R Ostlander, M C, Commanding Dr Bruce K Wiseman, "The Leukopenic and Leukemic States—Their Differentiation and Therapy" Presentation of Cases from the Medical Service Capt Victor H Kugel, M C—"Aplastic Anemia" Capt Newell W Howe, M C—"Purpura" Dr Charles A Doan, "The Anemic State—Its Recognition, Importance, Various Causes and Specific Treatment" Round Table Symposium, Major Arthur E Rappoport, M C, Presiding

#### WAR-TIME GRADUATE MEDICAL MEETINGS

REGION No 3 (New York)—Dr O R Jones, Chairman, Dr N Jolliffe, Dr H W Cave

*Induction Center, Grand Central Palace, New York City, New York*

January 19 Diagnosis and Treatment of Malaria—Dr Henry E Meloney

January 26 Diagnosis of Ano-rectal Disease—Dr Max Cowett

(To be repeated on February 2)

February 9 Head Injuries—Dr Eli Jefferson Browder

(To be repeated on February 16)

REGION No 4 (Eastern Pennsylvania, Delaware, New Jersey)—Dr B P Widmann, Chairman, Dr J S Rodman, Dr S P Reimann

*U S Naval Hospital, Philadelphia, Pennsylvania*

- January 26 Common Mistakes in the Diagnosis and Treatment of Gastro-Intestinal Diseases—Dr H L Bockus  
 February 9 Edema and Dehydration—Dr F William Sunderman  
 February 23 The Esophagus and Its Diseases—Dr L H Clerf  
 REGION No 5 (Maryland, District of Columbia, Virginia, West Virginia)—Dr J A Lyon, Chairman, Dr C R Edwards, Dr C B Conklin

*Newton D Baker General Hospital, Martinsburg, West Virginia*

- January 22 Protein Metabolism—Dr John Scudder  
 February 5 Indications for Use of Sulfonamides and Penicillin—Dr Henry B Mulholland  
 The Psychoneuroses in War—Dr David C Wilson  
 February 19 Treatment of Patients with Paraplegia Due to War Injuries—Dr Donald Munro  
 Liver Diseases Seen in the Present War—Dr Wallace Yater

*A A F Regional Hospital, Langley Field, Virginia*

- January 26 Chemotherapy—Dr Henry B Haag  
 Dermatology—Dr Richard W Fowlkes

*U S Naval Hospital, Norfolk, Virginia*

- February 2 Nucleus Pulposus, Medical Aspect—Dr Lay Martin  
 Nucleus Pulposus, Surgical Aspect—Dr Francis J Otenasek  
 REGION No 8 (Western Pennsylvania, Ohio)—Dr C A Doan, Chairman, Dr P G Smith, Dr F M Douglass

*Cile General Hospital, Cleveland, Ohio*

- January 23 Polycythemia—Dr Russell H Haden  
 February 27 Technique of Closure of Colostomies—Dr Thomas E Jones

*Fletcher General Hospital, Cambridge, Ohio*

- January 18 Nutrition—Dr Tom Spies  
 Diabetes—Dr Cecil Striker

*An Base Hospital, Patterson Field, Dayton, Ohio*

- January 18 Therapy and Prevention of Rheumatic Fever—Lt Commander Alvin Coburn, (MC), USNR  
 February 21 Diagnosis and Surgical Treatment of Acute Cholecystitis—Dr George Heuer

*Station Hospital, Lockbourne Air Base, Ohio*

- January 18 Psychosomatic Medicine—Dr George T Harding

REGION No 14 (Indiana, Illinois, Wisconsin)—Dr W O Thompson, Chairman, Dr N C Gilbert, Dr W H Cole, Dr W D Gatch, Dr R M Moore, Dr H M Baker, Dr E R Schmidt, Dr E L Sevringhaus, Dr F D Murphy

*Gardner General Hospital, Chicago, Illinois*

- January 17 Conditions Affecting Glucose Metabolism  
 January 31 Brain and Spinal Cord Injuries

- February 14 Diseases of the Intestinal Tract—Medical and Surgical Diagnosis and Care  
 February 28 Plexus and Peripheral Nerve Injuries

*Station Hospital, Fort Sheridan, Illinois*

- January 17 Diseases of the Intestinal Tract—Medical and Surgical Diagnosis and Care  
 January 31 Plexus and Peripheral Nerve Injuries  
 February 14 Dermatological Diseases  
 February 28 Burns and Plastic Surgery

*Mayo General Hospital, Galesburg, Illinois*

- January 17 Dermatological Diseases  
 January 31 Burns and Plastic Surgery  
 February 14 Malignancies in the Army Age Group—Medical X-Ray and Surgical Diagnosis and Treatment  
 February 28 Endocrinology

*Vaughan General Hospital, Illinois*

- January 17 Malignancies in the Army Age Group—Medical X-Ray and Surgical Diagnosis and Treatment  
 January 31 Endocrinology  
 February 14 Virus and Rickettsial Diseases—Medical and Neurological Diseases and Treatment  
 February 28 Psychosomatic Medicine

*Camp Ellis, Illinois*

- January 17 Virus and Rickettsial Diseases—Medical and Neurological Diseases and Treatment  
 January 31 Psychosomatic Medicine  
 February 14 Wound Healing and Tendon Surgery  
 February 28 Mental Hygiene and the Prevention of Neuroses in War

*Chanute Field, Rantoul, Illinois*

- January 17 Repair of Bone in Fractures and Diseases  
 January 31 Arterial Vascular Disease—Traumatic Lesions  
 February 14 Blood Dyscrasias—Malaria—Filariasis  
 February 28 Diseases of the Kidneys—Uro-genital Tract

*Truax Field, Wisconsin*

- January 17 Head and Spine Injuries—Dr T C Erickson  
 January 31 Allergic States—Dr Theodore L Squier  
 February 14 Effects of Cold and Dampness, Frostbite—Colonel Irving S Wright  
 February 28 Heart Disease—Dr Chester M Kurtz

REGION No 16 (Missouri, Kansas, Arkansas, Oklahoma)—Dr F D Dickson, Chairman, Dr O P J Falk, Dr H H Turner

*Station Hospital, Roscrans Field, St Joseph, Missouri*

- February 15 Acute Respiratory Disease  
 Shock, Burns and Blood Derivatives

*Regional Hospital, Fort Riley, Kansas*

- January 25 Clinical Psychiatry  
Neurology  
February 15 Gastrointestinal Diseases  
X-ray Diagnosis

*Station Hospital, Army Air Field, Great Bend, Kansas*

- January 18 Venereal Disease and Urology  
Anesthesia  
February 8 Orthopedic Surgery  
Chemotherapy  
Physical Therapy

*Winter General Hospital, Topeka, Kansas*

- January 18 Gastrointestinal Diseases—Dr Carl R Ferris  
General Surgery—Dr Claude J Hunt  
February 22 Plastic and Maxillary Surgery—Dr Earl C Padgett  
Clinical Psychiatry—Dr G Leonard Harrington

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The Portland Academy of Medicine held its annual dinner meeting at the Heathman Hotel on the evening of December 14, 1944

The Academy was founded in 1906 for the purpose of aiding the Medical School Library and promoting desirable medical legislation in the State of Oregon. The Academy is made up of physicians and medical teachers in Portland and in Oregon. Total membership is 205. Of this group, 40 are in the Armed Forces. The functions of the Academy principally concern sponsoring three lectureships each year, presenting outstanding authorities in the various fields of medicine, aid to the University of Oregon Medical School Library, sponsoring of a Medical Research Foundation incorporated under the laws of the State of Oregon. This Foundation is organized to receive gifts for medical research and is administered by a committee made up of members of the Academy and prominent men of the State.

The program at the annual meeting consisted of an address by the president, Warren C Hunter, M D, Professor of Pathology at the University of Oregon Medical School. Dr Hunter outlined the development of the Medical School during the years 1919 to 1924, a period during which the School experienced a most rapid growth and development. The guest of honor was Dr Noble Wiley Jones, F A C P, who has practiced Internal Medicine in Portland since 1906.

The following papers were presented in his honor: "His Contribution to Scientific Medicine," Dr Laurence Selling, F A C P, Professor of Medicine, "His Contribution to Practice of Medicine," Dr Homer P Rush, F A C P, Associate Professor of Medicine, "His Contribution to Medical Education," Dr Olaf Larsell Professor of Anatomy.

During the past year the Academy has sponsored the following lectureships: March 9 and 10, "An Histological and Chemical Analysis of Precancerous Lesions" and "Factors in Ageing from Point of View of the Physician," Edmund V Cowdry, Ph D, Professor of Cytology, Washington University Medical School, Director of Research at Barnard Hospital Cancer Institute, May 18 and 19 "Criteria of Ovulation" and "The Sterility Problem," W T Pommerenke, Ph D, M D, Assistant Professor of Obstetrics and Gynecology, University of Rochester, October 11, "Malaria and Filariasis," L T Coggeshall, Comdr (MC)-V(S) USNR Marine Barracks, Klamath Falls, Oregon.

Plans for the coming year include lectures by Dr Herbert F Tiaut, Professor of Obstetrics and Gynecology at the University of California Medical School in San Francisco and by Dr Joseph Erlanger, Emeritus Professor of Physiology at Washington University Medical School in St. Louis

Dr John Severy Hibben (Associate) was elected President of the Pasadena-Alhambra branch of the Los Angeles County Medical Society at its annual meeting on December 19

Dr Richard H Freyberg, F A C P, formerly Director of Arthritis and the Special Clinic for Rheumatic Disease at the University of Michigan Hospital, Ann Arbor, accepted an appointment as Director of the Department of Internal Medicine, Hospital for Special Surgery, on September 1, 1944, and has been located there since. He will be responsible for the activities of the medical division, both in-patient and out-patient medical clinic, and will be responsible for the development of the clinical laboratory. It is planned to develop also an excellent research laboratory with a broad research program.

A C P REGIONAL MEETING, Arkansas, Eastern Texas, Louisiana, Mississippi and Tennessee—Peabody Hotel, Memphis, January 25–26, 1945

*Program*

WM C CHANEY, M D, F A C P

*General Chairman and Governor for Tennessee*

THURSDAY, JANUARY 25, 1945

MORNING SESSION

*Presiding Officer*

M D LEVY, M D, F A C P

*Governor for Texas*

- 9 00 Blood Plasma Protein Studies in Cardiac Edema  
GEORGE HERRMANN, M D, F A C P, Galveston, Tex
- 9 30 Underwater Physiotherapy as an Adjunct Measure in the Treatment of Impaired Function in Muscles and Joints (Motion Picture)  
GEORGE FLETCHER, M D, F A C P, Hot Springs National Park, Ark
- 10 00 Bacterial Endocarditis (Slides)  
EDGAR HULL, M D, F A C P, New Orleans, La
- 10 30 Neurasthenia  
T S HILL, M D, (by invitation), Memphis, Tenn

SYMPOSIUM ON MALARIA

- 11 00 Introduction  
W C COLBERT, M D, F A C P, Memphis, Tenn  
Master of Ceremonies  
R B WATSON, M D, (by invitation), Memphis, Tenn  
Clinical Pathology of Malaria  
L W DIGGS, M D, (by invitation), Cleveland, Ohio  
Clinical Manifestations of Malaria  
HENRY PACKER, M D, (by invitation), Memphis, Tenn

## Pathologic Physiology of Malaria

HARRY FELDMAN, M D, (by invitation), Captain, (MC), AUS, Memphis, Tenn

## Diagnosis and Treatment of Malaria

FRANKLIN MURPHY, M D, (by invitation), Lieutenant, (MC), AUS, Memphis, Tenn

2 30 LUNCHEON

## AFTERNOON SESSION

*Presiding Officer*

O C MELSON, M D, F A C P

*Governor for Arkansas*

2 00 Psychosomatic Concepts in Gastro-enterology

CHARLES T STONE, M D, F A C P, Galveston, Tex

2 30 Planning Our Post-War Health Program

FELIX J UNDERWOOD, M D, F A C P, Jackson, Miss

3 00 Retinal Changes in Vascular Diseases

E C ELLETT, M D, (by invitation), Memphis, Tenn

3 30 Observations on Peptic Ulcer in the Army

W F HOLLENBECK, M D, F A C P, Lieutenant Colonel, (MC), AUS, Memphis, Tenn

4 00 Motion Picture on Malaria (from the Departments of Preventive Medicine and Anatomy, The University of Tennessee College of Medicine, Memphis)

T S ELIOT, Ph D, (by invitation), Memphis, Tenn

## EVENING PROGRAM

## HOTEL PEABODY

7 15 P M —Reception and Cocktails

8 00 P M —Banquet (Informal)

*Toastmaster*

O W HYMAN, Ph D

Dean, The University of Tennessee College of Medicine, Memphis

*Address*

ERNEST E IRONS, M D, F A C P, President

American College of Physicians, Chicago, Ill

## Distinguished Guests

GEORGE C THOMAS, Rear Admiral, U S Navy, Officer in Charge of the Professional Division, Bureau of Medicine and Surgery, Washington, D C

HUGH I MORGAN, Brigadier General, U S Navy, Chief Consultant in Medicine, Washington, D C

LEROY E BURNEY, Medical Director, U S Public Health Service, District No 4, New Orleans, La

WALTER BAUER, Colonel, U S Army, Consultant in Medicine Eighth Service Command, Dallas, Tex



JAMES E PAULLIN, Regent, Atlanta, Ga  
 CHARLES T STONE, Regent, Galveston, Tex  
 C W DOWDEN, Chairman, Board of Governors, Louisville, Ky  
 E R LOVELAND, Executive Secretary, Philadelphia, Pa  
 L W DIGGS, Cleveland, Ohio  
 RUSSELL L HADEN, Cleveland, Ohio

### Governors of the College

JOHN G ARCHER, Greenville—Governor for Mississippi  
 WM C CHANEY, Memphis—Governor for Tennessee  
 EDGAR HULL, New Orleans—Governor for Louisiana  
 M D LEVY, Houston—Governor for Texas  
 O C MELSON, Little Rock—Governor for Arkansas

FRIDAY, JANUARY 26, 1945

### MORNING SESSION

#### *Presiding Officer*

JOHN G ARCHER, M D, F A C P

#### *Governor for Mississippi*

- 9 00 Chronic Constrictive Pericarditis Report of Four Cases (Lantern Slides)  
 CHARLES CHAMBERLAIN, M D, F A C P, Fort Smith, Ark  
 9 30 The Clinical and Roentgenographic Signs of Herniation of the Cervical  
 Intervertebral Disc  
 J E WHITELEATHER, M D, (by invitation) Memphis, Tenn  
 10 00 Histamine Headache  
 C W DOWDEN, M D, F A C P, Louisville, Ky  
 10 30 Significance of the Plasma Proteins  
 L A CRANDALL, M D, (by invitation), Memphis, Tenn

### CLINICAL PATHOLOGICAL CONFERENCE

- 11 00 Case Presentation  
 W C COLBERT, M D, F A C P, Memphis, Tenn  
 Clinical Discussion  
 CONLEY H SANFORD, M D, F A C P., Memphis, Tenn  
 General Discussion  
 Pathologic Findings  
 DOUGLAS H SPRUNT, M D, (by invitation), Memphis, Tenn  
 12 30 LUNCH

### AFTERNOON SESSION

#### *Presiding Officer*

EDGAR HULL, M D, F A C P

#### *Governor for Louisiana*

- 2 00 Observations on the Medical Program Sponsored by the Surgeon General  
 of the United States Navy  
 JAMES E PAULLIN, M D, F A C P, Atlanta, Ga

## 3 00 The Treatment of Rheumatoid Arthritis

RUSSELL L. HADEN, M D, F A C P, Cleveland, Ohio

A C P REGIONAL MEETING, OKLAHOMA CITY, February 23, 1945

Oklahoma, Kansas, Missouri, Western Texas, Nebraska

Lea A. Riely, M D, F A C P, General Chairman and Governor for Oklahoma

## Tentative Program

On February 22, the Oklahoma City Internists Club will present its program. That evening the Regional Dinner Meeting of the College will be held at the Oklahoma Biltmore Hotel, brief addresses will be made by Dr Ernest E. Irons, F A C P, Chicago, President of the College, by Captain Willard J. Riddick, (MC), U S N, District Medical Officer of the Eighth Naval District, New Orleans, as official envoy of the Surgeon General of the Navy, by Colonel Edgar V. Allen, (MC), A U S, F A C P, Consultant in Medicine of the Seventh Service Command of the Army, Omaha, as official envoy of the Surgeon General of the Army.

The scientific program for February 23 will be as follows: "Usual and Unusual Gastrointestinal Radiology," Dr G. M. Tice of the University of Kansas, "Rheumatic Fever," Dr Don Carlos Peete, of the University of Kansas, "Asthma," Dr Harry Alexander, St. Louis, "Role of Calcium Metabolism in Circulatory Disease," Dr Graham Asher, Kansas City, "Arthritis," Colonel Edgar V. Allen, Omaha, "Penicillin," Major Carl Dietrick, Borden General Hospital, Chickasha, "Some Observations on Thiouracil," Dr Homer A. Ruprecht, Tulsa, "Acute and Chronic Local Ventricular Ischemia," Dr R. G. Bayley, Oklahoma City, titles yet to be announced by Dr Henry Turner, Oklahoma City, Dr O. C. Melson, Little Rock, Dr M. D. Levy, Houston, Capt Willard J. Riddick, New Orleans, Col. Walter Bauer, Dallas, and Major General David N. W. Grant, Washington.

Cooperating with the Chairman are the College Governors for Kansas, Dr Harold Jones, for Missouri, Dr Ralph Kinsella, for Texas, Dr M. D. Levy, for Nebraska, Dr Warren Thompson.

At a meeting of the Board of Regents at Philadelphia, December 16, 1944, the following elections to membership in the College were made.

## ELECTIONS TO ASSOCIATESHIP

Amtman, Leo, Chicago, Ill	Beard, Edmund Earl, Cleveland, Ohio
Appelman, Howard Benjamin, Detroit, Mich	Bell, James Roeder, Cleveland, Ohio, (MC), AUS
Ashe, William Francis, Jr, Cincinnati, Ohio, (MC), AUS	Bohrer, John James, Minneapolis Minn
Atwater, John Spencer, Rochester Minn, (MC), USNR	Boikan, William Clair, Chicago Ill
Autry, Daniel Hill, North Little Rock, Ark, (MC), AUS	Bortz, Donald Worcester, Cleveland, Ohio, (MC), USNR
	Brannon, William Tappan, New Orleans, La
Baldwin, Robert Sherman, Marshfield Wis, (MC), AUS	Brewen, Stewart Ferdinand, Wormlewsburg, Pa, (MC), AUS
Barnum, Glenn Lewis, Pasadena, Calif (MC), USNR	Brownley, Harvey Christian, Lynchburg, Va, (MC) AUS
Bean, William Bennett Cincinnati Ohio (MC), AUS	Brownstein Samuel R, New York, N Y, (MC), AUS

Cain, James Clarence, Rochester, Minn,  
(MC), AUS

Callaway, James Willis, La Jolla, Calif,  
(MC), AUS

Cecil, Richard Colbert, Richmond, Va

Chapman, William Holmes, Jr, Suffolk,  
Va, (MC), AUS

Cheskin, Louis Joseph, Newark, N J,  
(MC), AUS

Churukian, Giragos Missak, Paris, Ill

Cogan, Michael Aaron, Holyoke, Mass,  
(MC), AUS

Cohen, Aaron, Brooklyn, N Y

Comanduras, Peter Diacoumis, Detroit,  
Mich

Conway, William Hynes, New Rochelle,  
N Y, (MC), AUS

Cook, Joseph Russell, Huntington, W  
Va, (MC), AUS

Coombs, Frederick Stanley, Jr, Youngs-  
town, Ohio, (MC), AUS

Darnall, Charles Milton, Austin, Tex,  
(MC), AUS

Davie, John Holmes, Philadelphia, Pa,  
(MC), AUS

Davis, Hal, Roanoke, Va, (MC), AUS

Day, Hughes Winfield, Kansas City,  
Kan

Dolkart, Ralph Elson, Chicago, Ill

Drake, Ellet Haller, Detroit, Mich,  
USPHS (R)

Dunham, Charles Little, Chicago, Ill,  
(MC), AUS

Durkin, John Keenan, Bryn Mawr, Pa,  
(MC), USNR

Erickson, Eldon Wesley, Detroit, Mich

Ershler, Irving Leonard, Syracuse,  
N Y

Everett, Peter, III, New Orleans, La,  
(MC), AUS

Farmer, Charles Hall, Macon, Ga

Feffer, James Joseph, Washington, D C

Fenichel, Nathan Milton, Brooklyn,  
N Y

Finkelstein, David, Philadelphia, Pa,  
(MC), AUS

Flynn, Joseph Eugene, Iowa City, Iowa,  
(MC), AUS

Friedland, Elmer, Buffalo, N Y,  
(MC), AUS

Friedman, Maurice Harold, Chicago,  
Ill, (MC), AUS

Frisch, Robert Abraham, Milwaukee,  
Wis, (MC), AUS

Frist, Thomas Fearn, Nashville, Tenn,  
(MC), AUS

Fruchter, Harold, Long Island City,  
N Y

Geddis, James Thomas Joseph, New  
York, N Y, (MC), AUS

Gelbach, Philip Delmont, Detroit, Mich

Glenn, Paul Mitchell, Cleveland, Ohio,  
(MC), AUS

Glidden, Henry Spencer, Tewksbury,  
Mass, (MC), USNR

Goldstein, Milton Joseph, Scranton, Pa,  
(MC), AUS

Goldstein, Philip, New York, N Y,  
(MC), AUS

Gray, Joel Boyd, New Orleans, La

Gray, Seymour Jerome, Chicago, Ill

Grier, George Smith, III, Newport  
News, Va, (MC), AUS

Grishaw, William Harry, Los Angeles,  
Calif, (MC), AUS

Harris, Hilbert Lawrence, Syracuse,  
N Y

Hassett, Florence Sullivan, Elmira,  
N Y

Herndon, James Henry, Dallas, Tex,  
(MC), AUS

Hiller, Glenn Ivan, Detroit, Mich

Hinnant, Iredell Melvin, Cleveland,  
Ohio, (MC), AUS

Hoffman, Byron Jay, Atlanta, Ga,  
(MC), AUS

Holden, Lawrence Wheelock, Boulder,  
Colo

Hollands, Robert Arthur, Pasadena,  
Calif, (MC), AUS

Humphrey, Arthur Allan, Battle Creek,  
Mich, (MC), USNR

Hurevitz, Hyman M, Davenport, Iowa,  
(MC), AUS

Israel, Harold Louis, Philadelphia, Pa,  
(MC), AUS

Johnson, V(asey) Marklyn, West Palm  
Beach, Fla

- Kammerer, William Henry, New York, N Y, (MC), AUS
- Kaplan, Bernard Irving, New York, N Y, (MC), AUS
- Kaplan, George, Woodside, L I, N Y, (MC), AUS
- Kaufman, Benjamin, Brooklyn, N Y
- Kavee, Julius, New York, N Y
- Keinigsberg, Aaron, Chicago, Ill
- Kilhan, Dorothea Maria, Philadelphia, Pa
- Kinney, Robert John, Madison, Wis
- Kirsner, Joseph Barnett, Chicago, Ill, (MC), AUS
- Kirstein, Melvin B, St Louis, Mo, (MC), AUS
- Klainer, Max Joseph, Stoneham, Mass, (MC), AUS
- Klosk, Emanuel, Newark, N J
- Knowlton, Richard Stanley, Cleveland, Ohio, (MC), AUS
- Kopp, Israel, Boston, Mass, (MC), AUS
- Kossmann, Charles Edward, New York, N Y, (MC), AUS
- Kramm, Philip, New York, N Y, (MC), USNR
- Krieger, Edward Myers, Wilmington, Del
- Learner, Norman, Philadelphia, Pa, (MC), AUS
- Lee, Joseph Howard, Hamilton, Ont, Can
- Lefebvre, Edward James, Galveston, Tex
- Levy, Charles, Wilmington, Del
- Levy, Joseph, New Rochelle, N Y, (MC), AUS
- Lieder, Louis Eugene, Cleveland, Ohio, (MC), AUS
- Lief, Victor Filler, Far Rockaway, N Y, (MC), AUS
- Lindahl, Wallace William, Rochester, Minn, (MC), AUS
- Lipton, Harry Robert, Atlanta, Ga, USPHS (R)
- Litwms, Joseph New York, N Y, (MC), AUS
- Lozner, Eugene Leonard, Boston, Mass, (MC), USNR
- Lutz, Edgar Harvey Montrose, Pa, (MC), AUS
- Macdonald, Hugh, Glenview, Ill, (MC), AUS
- Macdonald, William Charles, St Louis, Mo
- MacNiel, Alec Cameron, Cleveland, Ohio, (MC), AUS
- Madsen, H(enry) Vernon, Detroit, Mich
- McDaniel, Lewis Tillman, Boston, Mass, (MC), AUS
- McLaughlin, James Alphonsus, Boston, Mass, (MC), USNR
- McLachlin, Ralph Edwin, Little Rock, Ark, (MC), USNR
- McNitt, Harry Arnold Hull, Washington, D C
- Medoff, Joseph, Philadelphia, Pa, (MC), AUS
- Menefee, Elijah Eugene, Jr, Durham, N C
- Miller, John Fleck, Newark, Ohio, (MC), AUS
- Mills, Charles Selby, Phoenix, Ariz, (MC), AUS
- Moench, Louis Gardner, Salt Lake City, Utah
- Moloney, William Curry, Boston, Mass, (MC), AUS
- Monaco, Thomas Clifford, Boston, Mass, (MC), AUS
- Moody, Rollen Wayne, Denver, Colo
- Myerson, Samuel, New York, N Y, (MC), AUS
- Myhre, William Norwood, Spokane, Wash, (MC), USNR
- Norman, James Kindred, New Orleans, La, USPHS (R)
- O'Connell, William Joseph, Jr, Detroit, Mich
- Offutt, Vernon Delmas, Kinston, N C
- Olsen, Alonzo Young, Los Angeles, Calif, (MC), AUS
- Page, Sidney Grey, Jr, Richmond, Va, (MC), AUS
- Paull, Ross, La Jolla, Calif, (MC), AUS
- Penner, Sidney Lincoln, Stratford, Conn, (MC), AUS
- Pfeiffer, Mildred Clara Julia, Philadelphia Pa

- Pignataro, Frank P, Marlboro, N J, (MC), AUS  
 Porter, Reno Russell, Boston, Mass, (MC), AUS  
 Post, Joseph, New York, N Y, (MC), AUS  
 Priddle, William Welmor, Toronto, Ont, Can, RCAMC
- Randall, William Spears, Jr, Pensacola, Fla, (MC), AUS  
 Ranges, Hilmer Albert, New Rochelle, N Y  
 Ray, Edward Scott, Richmond, Va  
 Raynolds, Arthur Hidden, New York, N Y, (MC), AUS  
 Read, William Alexander, Cleveland, Ohio, (MC), AUS  
 Redish, Jules, Lynbrook, L I, N Y  
 Roberts, Joseph Thomas, Washington, D C  
 Robertson, Alexander David, Willard, Ohio, (MC), AUS  
 Rosenberg, David Harry, Chicago, Ill, (MC), USNR  
 Rueger, Milton Jerome, Detroit, Mich, (MC), AUS
- Sauer, William George, Rochester, Minn, (MC), AUS  
 Scheifley, Charles Holland, Rochester, Minn, (MC), AUS  
 Schmidt, Richard Hermann, Jr, State-san, Wis  
 Shillito, Frederick Hopkins, New York, N Y  
 Shuler, James Benjamin, Washington, D C, (MC), U S Navy  
 Sittler, William Walter, Chicago, Ill, (MC), USNR  
 Smith, Richard Henry, Washington, D C, USPHS  
 Spruey, Russell Jordan, Indianapolis, Ind, (MC), AUS  
 Spurr, Charles Lewis, Chicago, Ill  
 Staris Robert Alphonsus, Ottawa, Ont, Can  
 Steele, George Chapin, West Springfield, Mass
- Storey, William Edward, Columbus, Ga, (MC), AUS  
 Stuart, Byron McClellan, New Orleans, La  
 Sullivan, William John, Bronxville, N Y, (MC), USNR  
 Suter, James Marion, Bristol, Va, (MC), AUS  
 Sweigert, Charles Francis, San Francisco, Calif, (MC), AUS
- Taylor, Robert Dewey, Indianapolis, Ind  
 Townsend, Stuart Ross, Montreal, Que, Can  
 Turner, Oliver Edmonds, Pittsburgh, Pa  
 Tweddell, John Thomson, Kingston, Ont, Can
- Vance, William Clifford, Richmond, Ind, (MC), AUS  
 Van Ormer, William Alfred, Cumberland, Md, (MC), AUS
- Walker, Douglass Willey, New Haven, Conn, (MC), AUS  
 Wallace, Joseph James, Washington, D C, (MC), AUS  
 Waller, William Kennedy, Baltimore, Md, (MC), AUS  
 Waud, Sydney Peyster, Chicago, Ill, (MC), AUS  
 Weinstock, Samuel, Brooklyn, N Y  
 Wendkos, Martin Howard, Philadelphia, Pa, (MC), AUS  
 Wever, George Kuhn, Stockton, Calif, (MC), AUS  
 Whinnery, Randall Allen, Detroit, Mich  
 White, Benjamin Vroom, Hartford, Conn, (MC), USNR  
 Whitehead, Duncan, Utica, N Y, (MC), AUS  
 Wilcox, Charles Frederick, Ottawa, Ont, Can  
 Williams, John Ralston, Jr, Winston-Salem, N C  
 Williams, Robert Hardin Boston, Mass  
 Wink, Irving Wolfe, Washington, D C

Winsor, Travis, New Orleans, La  
 Wolfram, Julius, Dallas, Tex., (MC),  
 AUS  
 Wood, William Hoge, Jr, Charlottes-  
 ville, Va., (MC), AUS

Worsley, Thomas Luther, Jr, Baltimore,  
 Md, (MC), AUS  
 Wosika, Paul Henry, Chicago, Ill  
 Zavod, William Abraham, Mount Ver-  
 non, N Y., (MC), AUS

## ELECTIONS TO FELLOWSHIP

Abbott, Gordon Arthur, Washington,  
 D C, USPHS

Adlersberg, David, New York, N Y  
 Alden, Ruel Lawrence, Hempstead, N  
 Y, (MC), AUS

Allan, Warde Baunton, Baltimore, Md  
 \*Allen, Raymond Bernard, Chicago, Ill  
 Altschul, Alexander, New York, N Y

Bagwell, John Spurgeon, Dallas, Tex.,  
 (MC), AUS

Barry, George Newton, Oklahoma City,  
 Okla

Bates, Robley Dunghison, Jr, Richmond,  
 Va., (MC), AUS

Baxmeier, Robert Ivan, Pittsburgh, Pa  
 Beckh, Walter, San Francisco, Calif

Beeman, Carl Burritt, Grand Rapids,  
 Mich, (MC), AUS

Bell, Robert A, Washington, D C,  
 (MC), U S Navy

Bellet, Samuel, Philadelphia, Pa

Benson, Kenelm Winslow, Berkeley,  
 Calif

Blankfort, Gerald, Little Rock, Ark,  
 (MC), AUS

Blumenthal, Jacob Solomon, Minneapo-  
 lis, Minn

\*Boyer, Norman Howard, Boston, Mass.,  
 (MC), AUS

\*Brown, Clarence Frank Gunsaulus, Chi-  
 cago, Ill

Brown, Madelaine Ray, Boston, Mass

Brown, Robert Whitcomb, Fort Steila-  
 coom, Wash

Carroll, Hubert Henry, Washington,  
 D C, (MC), U S Navy

Chaikin, Nathan Wolf, New York,  
 N Y

Charney, Louis Harry, Oklahoma City,  
 Okla, (MC), AUS

Chasnoff, Julius, New York, N Y  
 (MC), AUS

Chester, William, Mamaroneck, N Y,  
 (MC), AUS

Clifford, Milton Henry, Boston, Mass.,  
 (MC), AUS

Closson, James Harwood, Philadelphia,  
 Pa., (MC), USNR

Coggin, Charles Benjamin, Los Angeles,  
 Calif, (MC), AUS

Cook, Katharine Stewart, Troy, N Y  
 Crone, Neil Louis, Boston, Mass.,  
 (MC), AUS

\*Dow, Robert Stone, Portland, Ore  
 Drewyer, Glenn Edward, Flint, Mich,  
 (MC), USNR

\*DuBois, Franklin Smith, New Canaan,  
 Conn

Dugan, William Miller, Indianapolis,  
 Ind

Engbring, Gertrude Mary, Chicago, Ill

Faison, Elias Samson, Charlotte, N C  
 Fidler, Roswell Schiedt, Columbus, Ohio

Finkelstein, William, Waterbury, Conn  
 Fitts, Ralph Lamar, Grand Rapids,  
 Mich, (MC), AUS

Flinn, Robert Harrold, Washington,  
 D C, USPHS

Freyberg, Richard Harold, New York,  
 N Y

Friedlander, Richard Dufficy, San Fran-  
 cisco, Calif, (MC), AUS

\*Friend, Dale Gilbert Forrestt, North  
 Attleboro, Mass., (MC), AUS

Gibbons, Marion Noville, Cleveland,  
 Ohio

\*Gilbert, Newell Clark, Chicago, Ill  
 Glenney, Wilton Ross, Pottsville, Pa.,  
 (MC), AUS

Grieco Emil Henry, Bayonne, N J,  
 (MC), AUS

Harris, Alfred William, Dallas, Tex  
 Harris, Fred William, Little Rock, Ark  
 Hedgpeth, Edward McGowan, Chapel  
 Hill, N C

- Hiestand, Robert Forgy, Cincinnati, Ohio  
Helm, Standiford, Evanston, Ill, (MC), AUS  
\*Howard, Marion Edith, New Haven, Conn  
Howell, Llewelyn Pennant, Rochester, Minn  
\*Huber, Harry Lee, Chicago, Ill  
\*Jacobs, Henry Russell, Evanston, Ill  
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## OBITUARIES

### DR PHILIP FOSTER BARBOUR

Dr Philip Foster Barbour, M D, F A C P Born, Danville, Ky, February 24, 1867, A B (1884), A M (1900), Central University of Kentucky, M D, 1890, Hospital College of Medicine, now the University of Louisville, for many years, Clinical Professor, Diseases of Children, and head of the department, University of Louisville School of Medicine, from 1898 to 1908, Professor of Pediatrics, Hospital College of Medicine, Diplomate, American Board of Pediatrics, member and State Chairman, American Academy of Pediatrics, President, Kentucky State Medical Association, 1932, former President, Kentucky State Pediatric Society and Louisville Society for Mental Hygiene, Medical Chairman, Kentucky White House Conference, member, Association of American Teachers of Diseases of Children and Southern Medical Association, Fellow of the American Medical Association and American College of Physicians (the latter since 1920), Consulting Pediatrician, Kentucky State Department of Health and Kentucky State Baptist Orphan Asylum, formerly, Visiting Pediatrician, Louisville City Hospital, formerly, Consultant in Pediatrics, Kosair Crippled Children Hospital, Consulting Pediatrician and formerly Chief of Staff, Children's Free Hospital, Trustee, Centre College. died in St Anthony's Hospital November 1, 1944, age, 77

Dr Barbour was often referred to as the Dean of Southern Pediatrics and has probably trained more men in this specialty than any other individual in the South Dr Barbour was extremely active throughout his



entire life and the last few years of his practice were devoted almost entirely to the care of indigent children. His erect youthful figure was often seen on the golf courses where he usually humbled his younger opponents with a score in the 70's. Dignified, God-fearing, scholarly, and friendly to his conferees and patients alike, he will be greatly missed in the entire Southland.

C. W. DOWDEN, M.D., F.A.C.P.,  
Governor for Kentucky

### DR. JAMES PATRICK JORDAN

Dr. James Patrick Jordan (Associate), North Tonawanda, N. Y., died July 23, 1944, of bronchopneumonia at the age of 44.

Dr. Jordan was born on December 5, 1899. He received his Bachelor of Science degree at Canisius College in 1922, and his medical degree from the St. Louis University School of Medicine in 1932. After an internship of one year at the Sisters' Hospital, he spent two additional years as a Resident in the Millard Fillmore Hospital of Buffalo, and remained on the staff of that hospital for many years, having been Attending Physician at the time of his death.

Dr. Jordan was a Diplomate of the National Board of Medical Examiners, he did postgraduate work at Cook County Hospital, Chicago, and the Peter Bent Brigham Hospital, Boston. He entered the Medical Corps of the U. S. Naval Reserve on October 26, 1942, as Lieutenant Commander, and his death occurred in the South Atlantic Area, off the coast of South America.

Dr. Jordan was a very conscientious and enthusiastic worker and had gone a long way in his professional career. His passing is a great loss to Buffalo.

NELSON G. RUSSELL, SR., M.D., F.A.C.P.,  
Governor for Western New York

### DR. FREDERICK CASPER RINKER

Dr. Frederick Casper Rinker of Norfolk, Virginia, died on November 15, 1943. Dr. Rinker was born in Upperville, Virginia, on May 30, 1885. His academic education was acquired at Roanoke College, Virginia, where he received his Bachelor of Arts degree in 1906. In 1911 he graduated from the Department of Medicine of the University of Virginia and shortly became Resident Physician at the Philadelphia Polyclinic Hospital, where he remained for a year. Later, he became Assistant Physician at the Pennsylvania Hospital for Nervous and Mental Diseases, Philadelphia, remaining through 1912. The University of Wisconsin Medical School then claimed his services as instructor in Clinical Medicine, 1913-1914, Assistant Professor of Clinical Medicine, 1915-1919.

In the last named year, Dr Rinker moved to Norfolk, Virginia, where he remained until the time of his death. Dr Rinker was one of Norfolk's prominent physicians, a member of the Staff of the Norfolk Protestant Hospital, the Lee Memorial Hospital, and the Norfolk General Hospital. As Former Treasurer of the Seaboard Medical Association, Past President of the Southside Medical Association, Member of the Norfolk County Medical Society, Virginia State Medical Society, American Medical Association, Fellow of the American College of Physicians since 1922, and a Diplomate, American Board of Internal Medicine, he fully proved his true interest in the field of Internal Medicine.

During the first World War, Dr Rinker was a First Lieutenant in the R O T C, University of Wisconsin (Contract Surgeon). In 1935, he was appointed Lieutenant Commander in the U S Naval Reserve.

Dr Rinker always displayed a keen and lively interest in the problems of Internal Medicine. He was active in the medical society of his state and always had a bright and cheering word, tinged with pertinent observation. His death seems particularly untimely owing to the fact that his energy and enthusiasm had changed so little with the advancing years. His friends will miss him. His wife, two brothers and a sister survive.

J EDWIN WOOD, JR, M D, F A C P,

Governor for Virginia.

### DR ROBERT LENOX BARNES

Dr Robert Lenox Barnes, an Associate of the American College of Physicians, was born in Washington, C H, Ohio, May 19, 1886, and died at his residence, 1337 Bryden Road, Columbus, Ohio, on August 3, 1944. Dr Barnes graduated from the College of Medicine of the Ohio State University in 1910. Soon after his graduation he became a member of the teaching staff of his Alma Mater, and for a time was an instructor of Clinical Pathology. His practice was limited to Internal Medicine paying particular attention to diseases of the cardio-vascular system, and to the treatment of arthritis.

He was Chief of Staff of Mt Carmel Hospital, with which institution he had been connected since his graduation. In addition to being an Associate of the College he was a member of the Columbus Academy of Medicine, Ohio State Medical Association, American Medical Association, American Heart Association and the American Society for the Study of Arthritis.

Dr Barnes was a student, and in this country took post-graduate work at Harvard University, Johns Hopkins University and New York Post-Graduate School of Medicine. He spent the years 1930 to 1932 at the University of Vienna, Austria. He made a special study of arthritis in London in 1934 and in 1936.

He was a member of the Nu Sigma Nu Medical Fraternity, a 32nd degree Mason and a Methodist. He was an active member of the Columbus Club and the Scioto Country Club.

Dr. Barnes was admired and held in high esteem by his colleagues, and because of his personal interest in his patients he endeared himself in their hearts. He will be greatly missed. His widow and a sister survive.

CHARLES W. MCGAVRAN, M.D., F.A.C.P.,  
Columbus, Ohio

### DR. A. COMINGO GRIFFITH

With the death of Dr. A. Comingo Griffith on November 9, 1944, the American College of Physicians lost a fine friend, and his many friends and associates in Kansas City, Missouri, a fine doctor.



A. COMINGO GRIFFITH, M.D., F.A.C.P., Kansas City, Mo.  
Former Governor and former Vice President, American College of Physicians

Dr. Griffith's influence extended far. After a preliminary education at Lawrenceville School and Princeton University, he obtained his degree in Medicine in 1906 at the University of Kansas. He added to this education much postgraduate work and entered a career in the practice of medicine well equipped to care for the sick. His interests led him into the best medical associations, local and national.

He became a Fellow of the American College of Physicians in 1922, and was a member of its Board of Governors from 1929 to 1942, and Third Vice-President 1942-1943. He helped to organize the Kansas City Southwest Clinical Society, was its President in 1936, and always worked for the success of its programs. He could be counted on to support every worthwhile medical project in his home city and elsewhere. He was a Diplomate of the American Board of Internal Medicine, a member of Jackson County Medical Society, Missouri State Medical Association, American Medical Association, and the Kansas City Academy of Medicine. He was most actively associated with St. Joseph Hospital.

Besides these public associations, there are the countless unrecorded associations carried in the affections of his friends and patients.

RALPH KINSELLA, M D , F A C P ,  
Governor for Missouri

### DR OSCAR MONROE GILBERT

Dr. Oscar Monroe Gilbert, F A C P , one of the outstanding internists of Colorado, died suddenly October 18, 1944, at his home in Boulder. Dr. Gilbert was born February 12, 1873, in Fulton, Missouri. In 1898 he graduated from the Barnes Medical College of St. Louis. His keen interest in keeping up with the advances of scientific medicine was reflected by frequent graduate work in such places as Johns Hopkins, Vienna, London and Munich, and his desire to impart scientific knowledge, by the fact that he was a member of the Faculty of the University of Colorado School of Medicine for thirty-four years. He was made Professor of Medicine, Emeritus, in that institution in 1934.

During his forty-four years as a resident of Boulder he found time for much activity in civic affairs. His professional activities were largely limited to the specialty of tuberculosis. He was President of the Colorado State Medical Society in 1913 and 1914. He served as a captain in World War I, and he is to be honored for his part in World War II for, in 1942, because of the shortage of civilian physicians, he returned to an active practice from which he had retired for many years.

In addition to his activities in County and State medical organizations and his Fellowship in the American College of Physicians, Dr. Gilbert was a Fellow of the American Medical Association and a member of the Denver Clinical and Pathological Society.

Besides his wife, Dr. Gilbert is survived by five children, three daughters and two sons, both of whom are physicians serving in the Armed Forces of the United States.

WARD DARLEY, M D , F A C P ,  
Governor for Colorado

## DR EDWARD LUTHER WHITNEY, F A C P

Dr Edward Luther Whitney of Walla Walla, Washington, was born in Chatham, Medina County, Ohio, in 1870. His general education was in the public schools of Chatham, he later attended Oberlin College. He graduated in medicine at Baltimore Medical College (now part of the University of Maryland) and received the degree of Doctor of Medicine in April, 1895. He was then appointed assistant resident physician and surgeon at the college hospital. After one year, he became resident pathologist for the Maryland General Hospital, serving there from 1896 to 1901. During this period, he was instructor in pathology in Baltimore Medical College, continuing until 1916, the year he came west. He first settled in Portland, Oregon, and engaged in general practice, but in January, 1918, he moved to Walla Walla, Washington, beginning a professional career that was marked for its distinction and success.

Throughout his residence in Walla Walla, Dr Whitney specialized in diagnosis and internal medicine, establishing an enviable reputation in this part of the State. He became a Fellow of the American College of Physicians in 1923. He was a Fellow of the American Medical Association, a member of the Washington State Medical Association, the Walla Walla County Medical Society (Past President), the American Chemical Society, and a Diplomate of the American Board of Internal Medicine.

When the war came, Dr Whitney had attained the age at which many men would have sought retirement, or at least a sharp reduction in the number of his responsibilities. Like a good soldier, however, he continued his practice, and until stricken with the illness that cost his life, he ministered to the ill. He died on September 13, 1944, in Walla Walla of cerebral hemorrhage, and his loss will be keenly felt.

E G BANNICK, M D, F A C P,  
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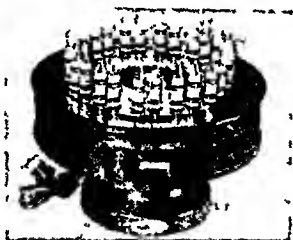
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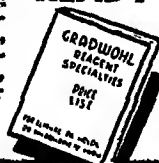


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- No. 1. **CARDIOLOGY**: Columbia University and Presbyterian Hospital, New York, Robert L. Levy, F.A.C.P., Director, 1 week, March 18-24
- No. 2. **MECHANICS OF DISEASE**: Harvard University and Peter Bent Brigham Hospital, Boston, George W. Thorn, F.A.C.P., Director, 2 weeks, April 9-21
- No. 3. **CLINICAL MEDICINE—HEMATOLOGY**: Ohio State University, Columbus, Charles A. Doan, F.A.C.P., Director, 1 week, April 16-21
- No. 4. **GASTRO-INTESTINAL DISEASES**: Graduate Hospital, Philadelphia, Henry L. Bockus, F.A.C.P., Director, 1 week, April 23-28
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Third edition, December, 1944, 447 pages, 41 plates, \$4 50

The first and most comprehensive survey in English of the clinical manifestations of vitamin deficiencies has proved of great service to the medical profession and this new third revised edition will be welcomed. The book has helped to clarify a field in which there were many exaggerated claims. Etiology, diagnosis, treatment and prevention are fully considered, based on authoritative interpretations of clinical observations, on examination of much pathological material, and on biochemical investigations by laboratory experiments. The text has been rearranged to sharpen the separation between the deficiency diseases and the chemical nature and function of the vitamins. The authors hope the discussion of the significance of vitamins as disease provokers does not convey an impression of omniscience. They subscribe to the sound point of view of the technical committees of the American Medical Association which they believe reflects the judgment of many clinicians. The chapters on the chemical nature of the vitamins and cellular oxidation have been rewritten and much new material added throughout the book including many new illustrations. If you want to be sure of knowing the truth about vitamins and vitamin deficiencies invest in a copy of Eddy and Dalldorf.

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#### CHAPTER

- I Introduction
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- IV Vitamin Requirements
- V The Nature and Function of Vitamin A
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- VIII The Nature and Function of Niacin
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- XX The Vitamin B Complex
- XXI Vitamin C Deficiency
- XXII Vitamin D Deficiency
- XXIII Vitamin E Deficiency
- XXIV Vitamin K Deficiency
- XXV The Vitamins and Infectious Diseases
- XXVI Medical Care of Nutritional Failure

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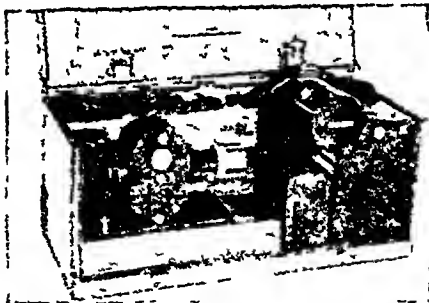
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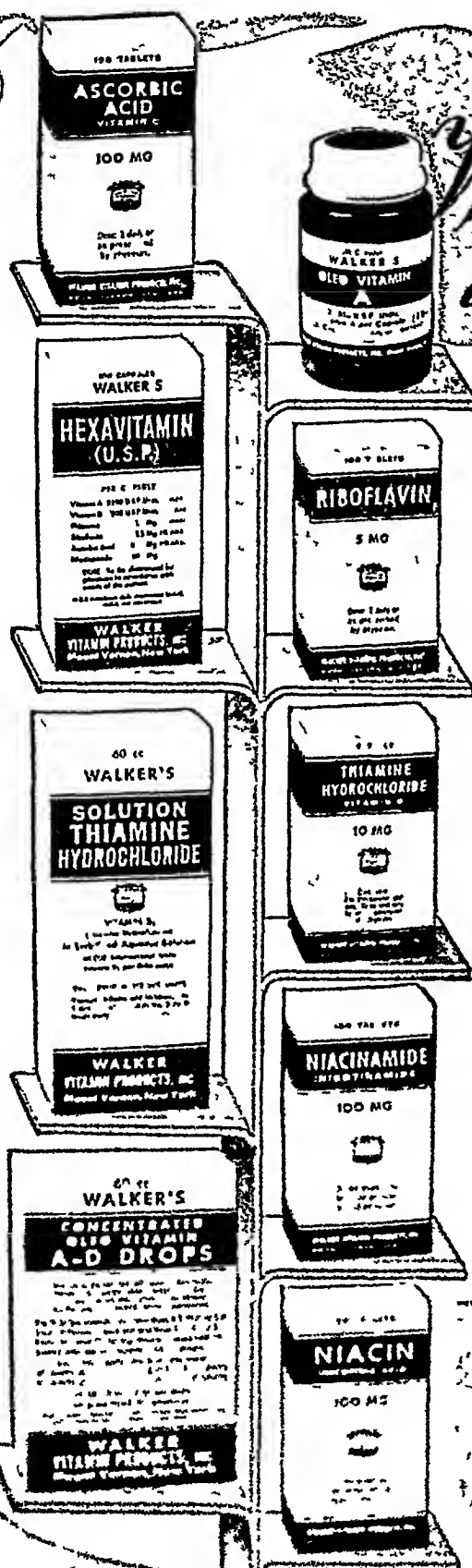
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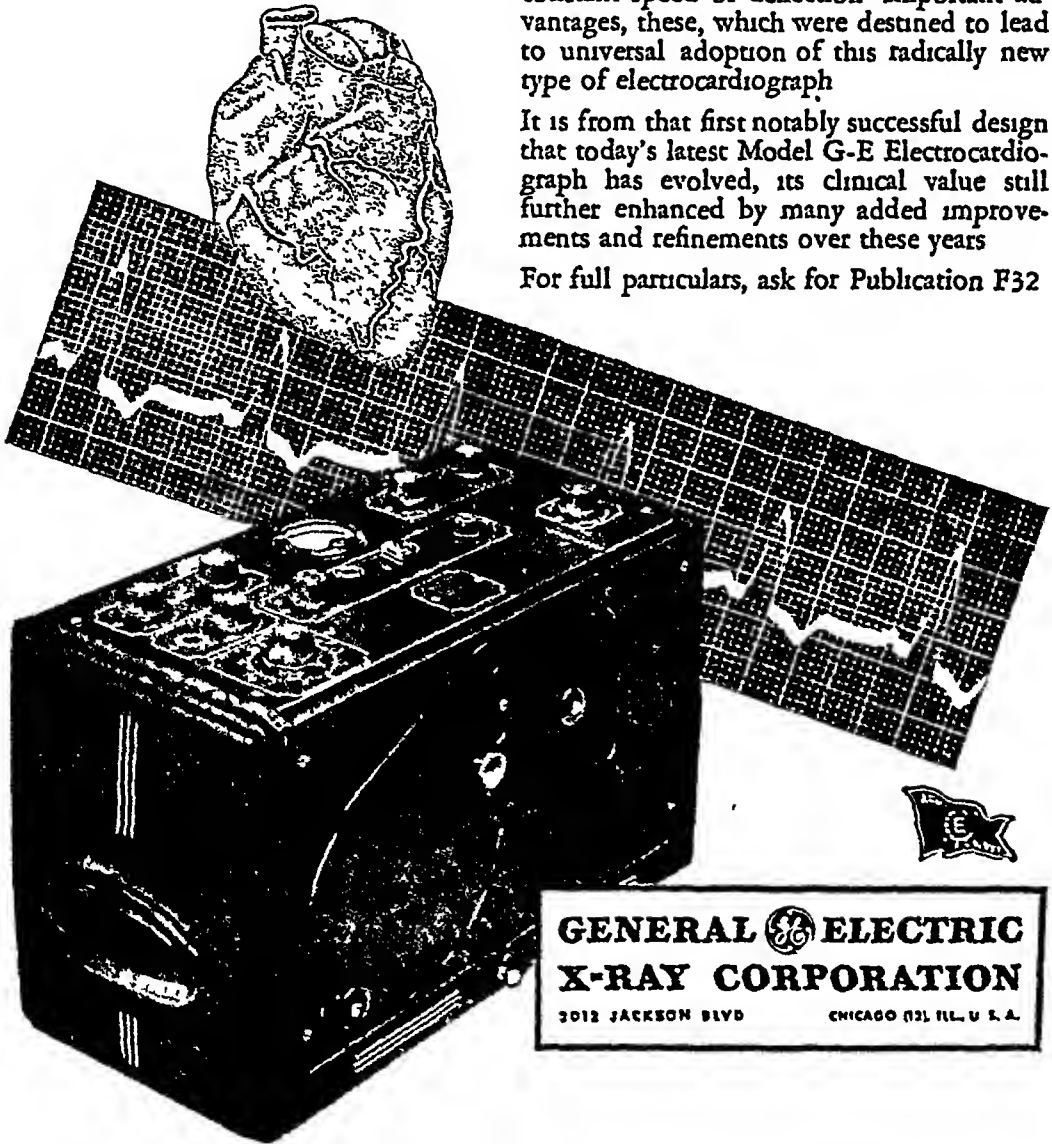
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**INDICATED** in the treatment of both spastic and atonic constipation and as an adjunct to dietary measures for the control of constipation in aged, convalescent and pregnant patients.

**DOSAGE** 1 or 2 teaspoonsful in a glass of water, milk, or fruit juice once or twice daily, followed immediately by another glass of liquid. It may also be placed on the tongue and washed down, or it may be eaten with other foods. Ample fluid intake is advisable to assure maximum bulk formation.

\*See H. J. T. 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100.

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**Pills Stramonium** (*Davies, Rose*)  
 $2\frac{1}{2}$  grains

Physicians in private practice as well as in neurological clinics have widely prescribed these pills since 1929, and their continued interest in and use of them points to the serviceability of this therapy.

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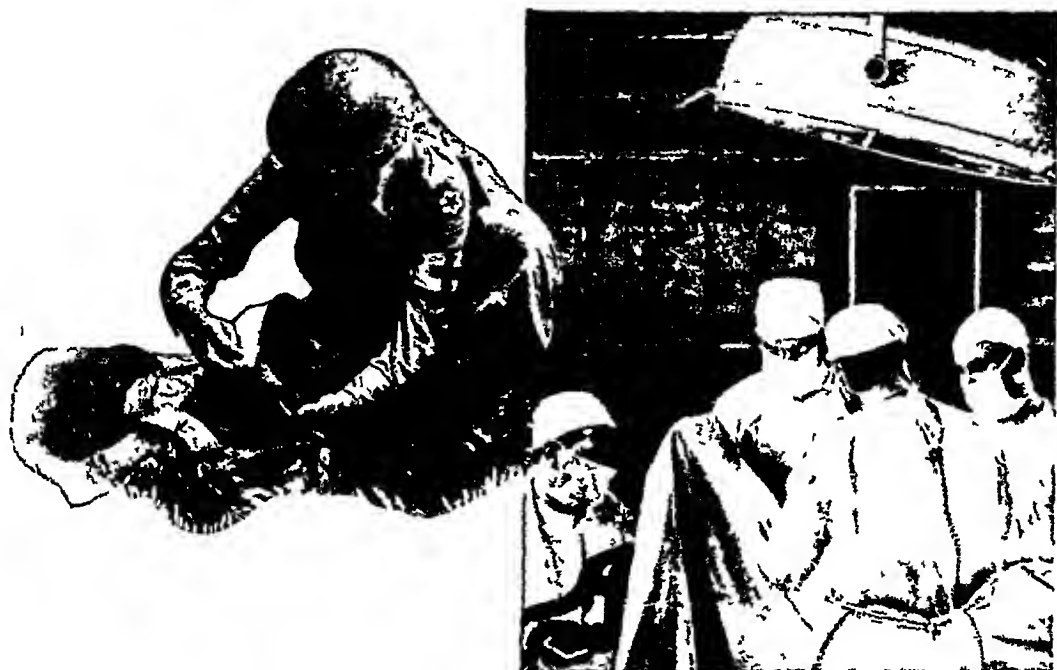
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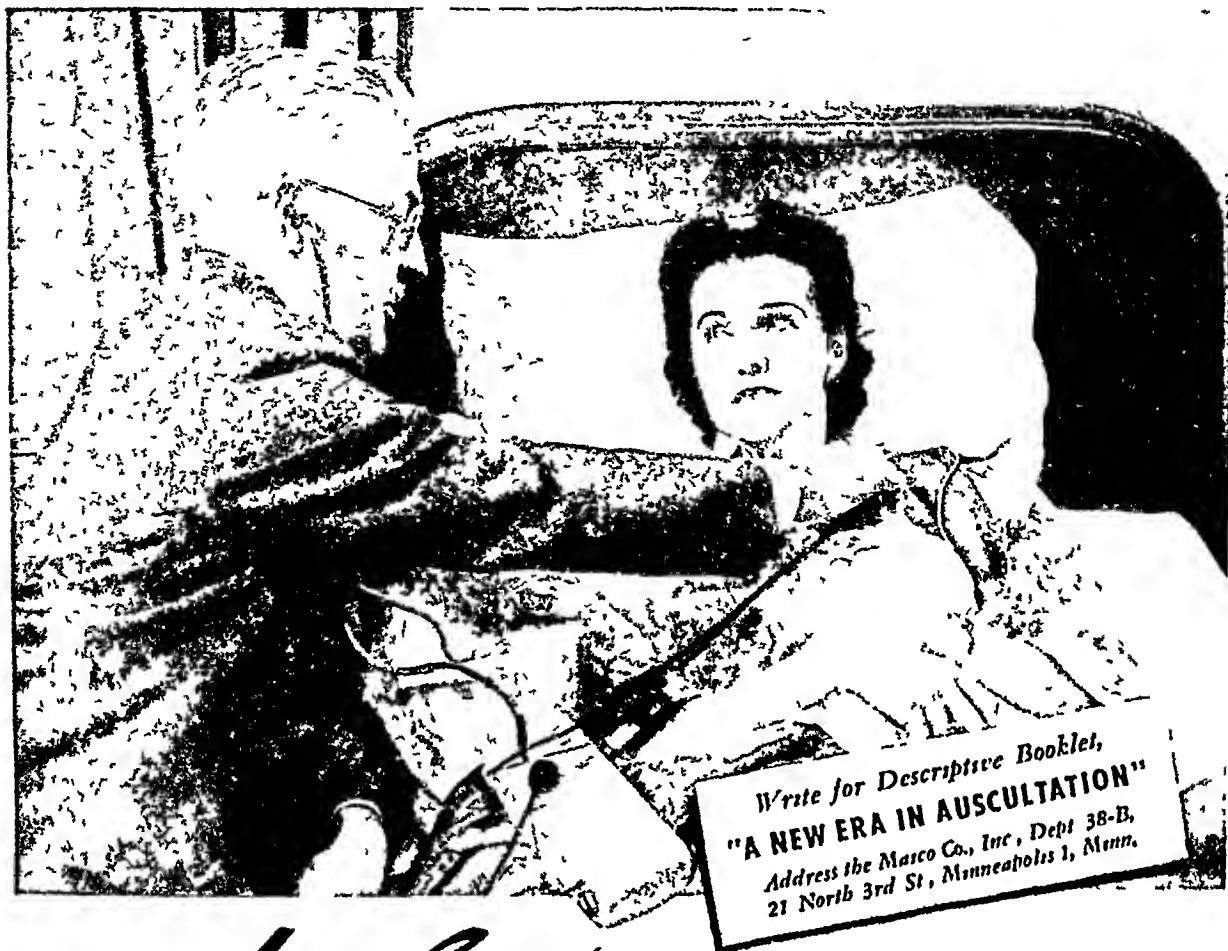
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The Stethetron not only intensifies body sounds, but enables the physician to emphasize particular sounds while subduing others. Rales and heart murmurs, extremely important in diagnosis but often scarcely distinguishable with an acoustic stethoscope, may be intensified many fold, and given greater relative prominence by subduing the normal heartbeat sounds. Both

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**W**HEN the patient is discharged from the hospital, every effort is used to encourage his continuing good dietary habits

To provide the incentive for the patient to persevere in the intake of a highly nutritious diet, an acceptable supplemental food should be advised

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is a well-balanced food, supplying biologically complete protein in addition to easily utilizable, partially predigested carbohydrate. Because it is so quickly digestible Horlick's does not interfere with the next full meal. It is delicious whether prepared with milk or water.

*Recommend* ~

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The Complete Malted Milk—Not Just a Flavoring for Milk

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Obtainable at all drug stores



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Dextrose  
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**"containing no  
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A medicinal specialty of WYETH Incorporated, Petrogalar Laboratories, Inc. Division, Philadelphia.

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FOR SAFE RETURN TO "HABIT TIME"



# Why You Can't Get

## SANBORN MEDICAL INSTRUMENTS

(Present or "Post War" Models)

### As Quickly As You Wish

**T**O the many physicians and hospitals who have ordered, or wish to order, SANBORN Medical Diagnostic Instruments, and have been told that, because of "war commitments," shipment can be made only after long and perhaps indefinite delay — detailed explanation is due.

Here are the facts:

Shortly after Pearl Harbor, this organization voluntarily enlisted. We offered our services to the United States Government for the design, development and manufacture of electrocardiographs, metabolism testers, or any other equipment, medical or non medical, that would, in their opinion, help win the war.

The offer was accepted.

Sanborn Company was assigned two lines of duty:

First, the continued manufacture of the "Instomatic" CARDIETTE and WATERLESS Metabolism Tester for use by medical branches of the Army and Navy. Second, the design, development and manufacture of radar and other communications devices for use by the Navy Bureau of Ships, the Army Signal Corps, and others.

Since that original assignment, Sanborn Company has manufactured and delivered to the Government many thousand CARDIETTES, WATERLESS Metabolism Testers, and radar units of various types — all destined to help win the war.

#### Ninety Percent on "War"

To accomplish this, ninety per cent of our productive effort was turned over to meeting war requirements — and that means emphasis still continues. Excess capacity of plant facilities, additional personnel, extra working shifts and all similar steps were also taken.

Meanwhile, the production and shipment of Sanborn medical instruments to civilian purchasers has had to come from the remaining ten per cent — frequently reduced by the percentage of material per cent of it to fill emergency war orders for a while.

#### Service to PRESENT Owners

After a period of adjustment, we have taken steps to ensure that present owners are not inconvenienced.

tain "service" — supplies and repairs — to present Sanborn owners. As one example, when stocks or some "supply" items have been dangerously low, new shipments of instruments using that item have been cancelled until the needs of present owners could be filled.

All this has meant delay — long-continued delay in some cases — in meeting civilian obligations for new equipment.

These are the facts in the situation to date.

#### When Can We Ship?

The patience of those who have placed their orders with us, and their evident willingness to "wait for a Sanborn instrument," have been most gratifying. Similarly so has been the interest of the many physicians and hospitals who continue to inquire regarding the availability of Sanborn electrocardiographs and metabolism testers.

To both groups, we would like to give a definite reply to the question, "When can my order for a Cardiette, or a Waterless Metabolism Tester be filled?"

Estimates or attempts to estimate are most unwise. War orders for medical equipment and for radar, continue to be placed with us in volume — and more frequently without advance notice than otherwise.

All we can reply is — "As quickly as our other duties permit."

The moment these duties are lightened — as quickly as limitations on materials and manpower (fully complied with by Sanborn Company) are lifted — civilian needs will be met. And, in the occasional "interludes" between war orders as many civilian Cardiettes and Waterlesses as possible will be released and shipped. If any "surplus" above war requirements can be achieved, these instruments also will immediately be shipped to civilian purchasers.

#### A Policy — A Citation

Such has been, and will continue to be, the Sanborn policy. We believe it to be fair.

And for those who are interested in the future of the medical instrument industry, we can say that Sanborn Company is determined to see that the industry is not left in a lurch.

In common with other manufacturers doing war work, our contracts have been subject to "renegotiation." After most searching investigation, made in this case by the Office of the Surgeon General, the renegotiators reported to us, in substance:

"We have studied carefully the record of your company in the war effort. We have checked your claims with the Office of the Surgeon General, Bureau of Ships, and all the government departments with whom you have had contact. Your contribution to radar designs has been so valuable, your cooperation with all government agencies has been so high, that we are happy to report that your record is outstanding."

#### What About "Post War"?

Many are asking, "Will Sanborn Company produce new and better electrocardiographs and metabolism testers after the war?"

The answer is yes — definitely yes.

Following another Sanborn policy — constant improvement and advancement in instrument making to keep pace with improvement and advancement in medicine — as much engineering thought and time as possible is being given to new developments along many lines.

The results of this work will be announced only when we are sure that the improved instruments will be acceptable and practical as well as new.

Progress to date, however, indicates that without question the "post war" Sanborn instruments will be well worth waiting for.

Meanwhile, those who purchase and receive a present Sanborn model can be assured on two important points:

The instrument they get will be among the best available, and exactly the duplicate in every important respect, of a present Sanborn apparatus.

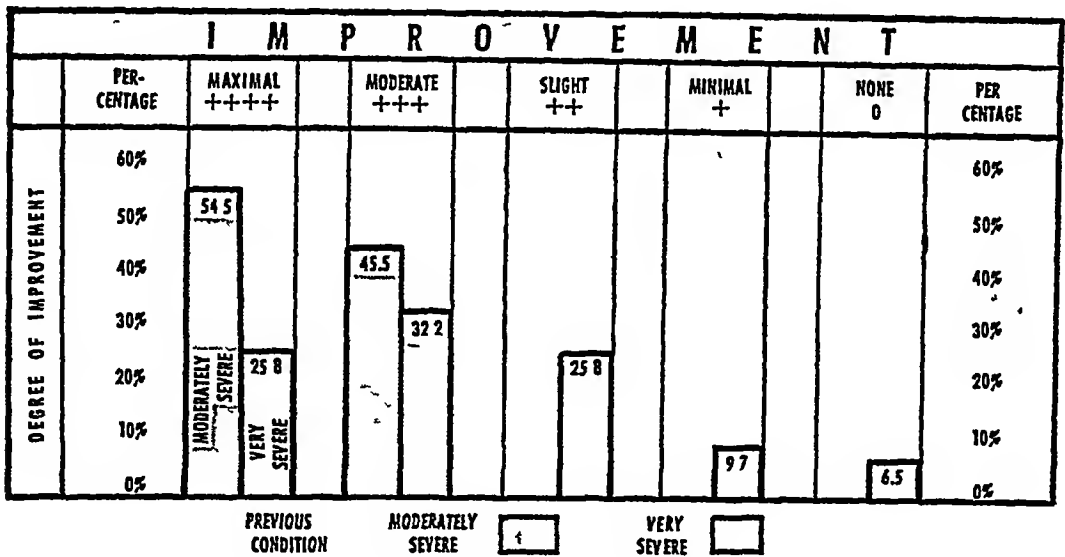
The trade-in value of their instrument. If later exchange for a "post war" model is desired, will be maintained at a fair level.

# SANBORN COMPANY

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*Significant percentage of Improvement* ---

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\*Fahling H D and Zeligs M A  
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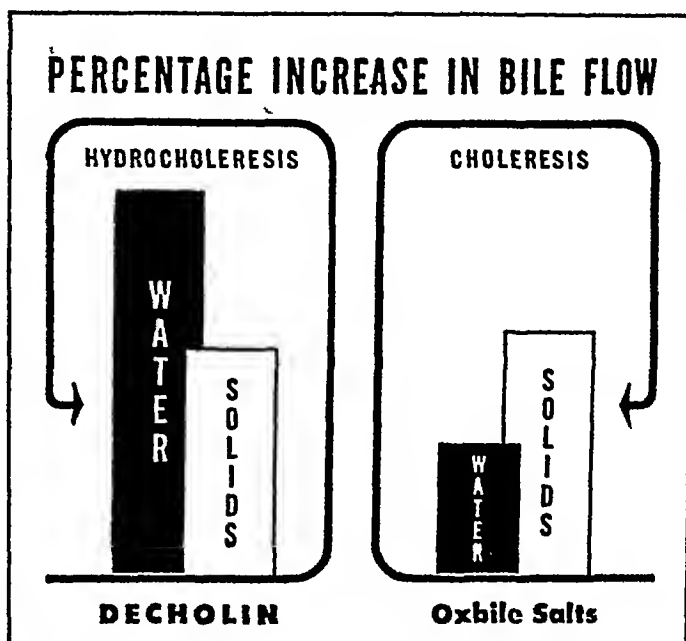


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NON-ALKALINE ANTACID THERAPY



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\*Reiter, P. J., Experience with Benzedrine, *Lancet*, 1934, 1:1100-1107



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Each tablet contains 5 mg.

SMITH, KLINE & FRENCH LABORATORIES, PHILADELPHIA, PA.

# WHEN MILK BECOMES "FORBIDDEN FOOD"

## SYMPTOMS

Persistent GI distress or  
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## DIAGNOSIS

Defect almost always  
allergy to cow's milk

## TREATMENT

Eliminate milk from diet  
Replace with suitable hypoallergenic substitute (Mull-Soy)

## COMPARATIVE COMPOSITION

1 Part Mull Soy		Average Whole
1 Part Water		Cow's Milk
31%	Protein	33%
40%	Fat	38%
4.5%	Carbohydrate	4.9%
10%	Total Minerals	0.7%
87.2%	Water	87.3%

Each provides 20 calories per fluid ounce



## MULL-SOY FOR EQUIVALENT NUTRITION

While the manifestations of milk allergy or intolerance are most often seen in infants they may be present at any age. And, when successful treatment demands complete elimination of milk from the diet, replacement by food approximately equivalent in nutritional elements becomes imperative.

MULL SOY is an effective hypoallergenic substitute for cow's milk—a concentrated, emulsified liquid soy bean food which closely approximates cow's milk in protein, fat, carbohydrate and mineral content. It is palatable, well tolerated, easy to digest, and easy to prepare. Infants particularly relish MULL SOY and thrive on it!

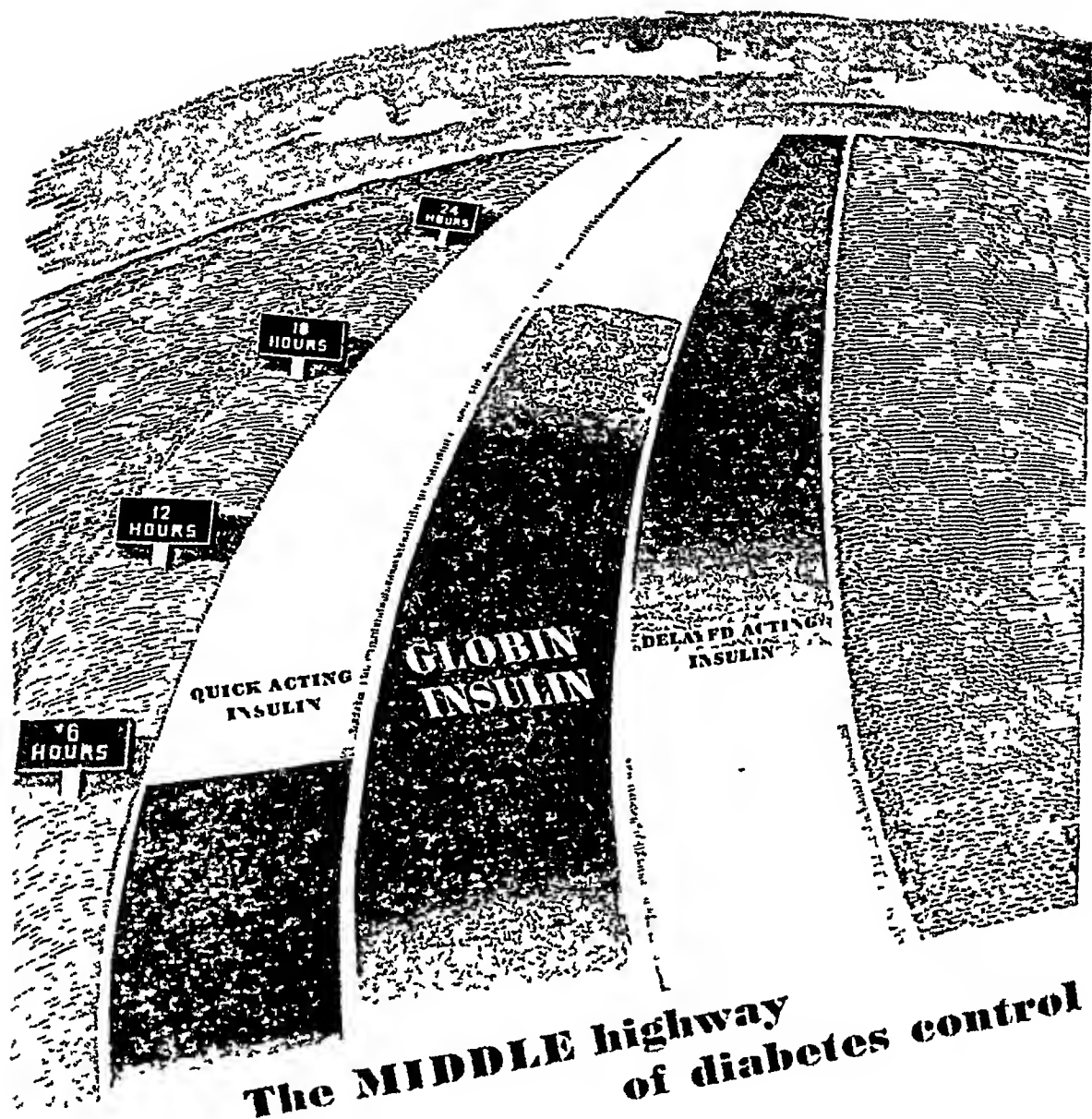
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## Hypoallergenic Soy Bean Food

MULL SOY is a quick tempered food prepared from soy bean flour, soy bean oil, dextrose, sucrose, calcium phosphate, calcium carbonate, salt and soy bean lecithin, homogenized and sterilized. Available in 1 1/2 lb. or 3 1/2 lb. cans at all drug stores.





## The MIDDLE highway of diabetes control

There are three main insulin roads upon which a physician may direct his patient toward diabetes control.

One insulin is quick acting but short lived. Another is slow acting but prolonged. Intermediate between these is 'Wellcome' Globin Insulin with Zinc—designed to meet many patients' needs.

The many patients whose diabetes is controlled by a single injection of Globin Insulin obtain the benefits of rapid onset of action, sustained daytime effect, and nighttime diminished action—which tends to minimize nocturnal insulin reactions.

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lergenic properties, is comparable to regular insulin. It is accepted by the Council on Pharmacy and Chemistry, American Medical Association, and was developed in the Wellcome Research Laboratories, Tuckahoe, New York. U.S. Patent No. 2,161,198. Available in vials of 10 cc, 80 units in 1 cc.

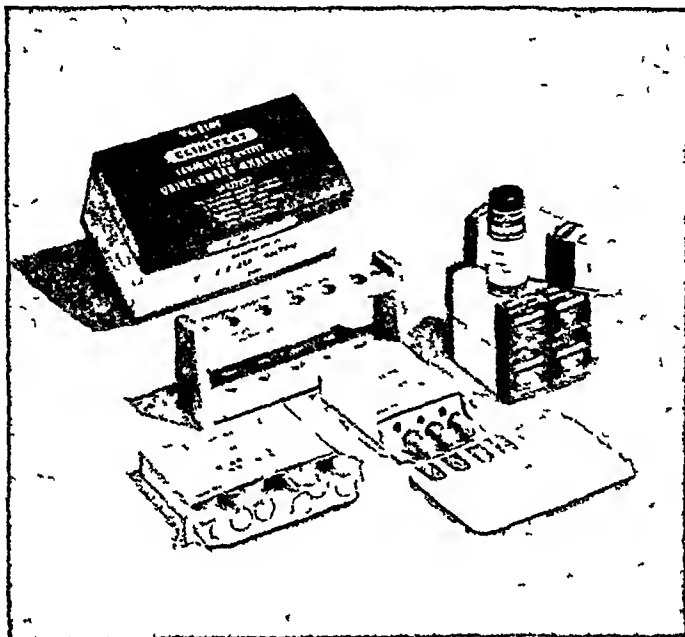
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A Standardized Method Requiring No External Heating



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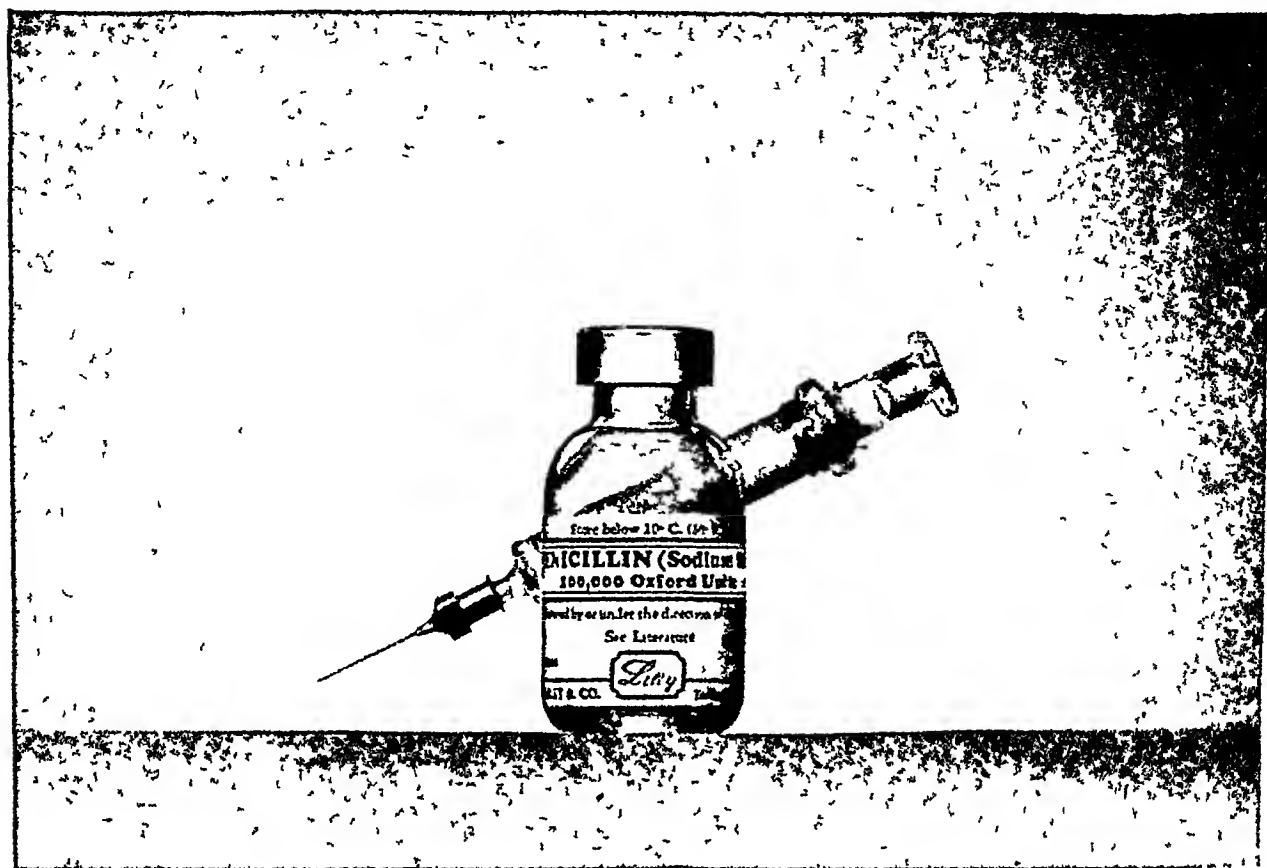
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Pablum is convenient because it requires no cooking. Thus, the patient can prepare his meal at the office or shop simply by adding milk at any temperature. Pablum absorbs about 12 times its own weight of milk, so that it offers a good vehicle for milk.

In ulcerative colitis and intestinal tuberculosis, Pablum has also been found useful in the dietary.

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Wheat Germ	15	Moisture	7.0
Cornmeal	10	Minerals (ash)*	4.2
Powdered Beef Bone (Specially prepared for human use)	2	Lip (ether extract)	3.0
Sodium chloride	1	Gross Fiber	0.9
Alfalfa Leaf	1	*Including	
Dried Brewers Yeast	1	Calcium	0.76%
Reduced Iron (11 Gm. per 100 lbs.)		Phosphorus	0.62
		Iron	0.01
		Copper	0.0014

Approx. caly 106 calories per oz. or 3.7 per Gm. 12 level tablespoonfuls = 1 oz.  
Each level spoonful contains not less than 0.3 mg. of vitamin B<sub>1</sub> and 1.0 I.U. of vitamin C.

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# ANNALS OF INTERNAL MEDICINE

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## THE TREATMENT OF ADDISON'S DISEASE BY THE IMPLANTATION METHOD<sup>\*</sup>

By C F KEMPER, M D, F A C P, *Denver, Colorado*

THE implantation of normal suprarenal glands or a potent extract of normal suprarenal glands has been foreshadowed since Addison's disease was first put on a sound clinicopathological basis in 1855. At that time, in his search for an explanation of idiopathic anemia, Thomas Addison as he said "stumbled upon the curious facts" that some asthenic patients of "dingy hue" were found at postmortem examination to have but one demonstrable pathological lesion and that was the destruction of the suprarenal capsules. Obviously he concluded that some significant relationship exists between the clinical syndrome and the pathological changes which he had so accurately observed. Thus and then was laid the first of the pillars upon which the scientific superstructure of replacement therapy of the endocrine glands has been erected.

So far, gland grafting, though rational and sound theoretically, has met only with failure when applied to the correction of suprarenal deficiency disease. Consequently, hope has been directed toward, first, gland extracts, second, isolation of, or synthesis of a potent hormone or hormones, and third, the implantation of compressed pellets of crystalline hormone compositions. However, the early adumbration of such a practical procedure remained untested and unverified for 75 years, when Hartman, MacArthur and Hartman,<sup>1</sup> Rogoff and Stewart,<sup>2</sup> and Swingle and Pfiffner,<sup>3</sup> working in separate groups and entirely independently, were all able to extract a substance which when injected into bilaterally adrenalectomized animals, manifested life-prolonging powers. These substances were soon purified, roughly standardized biologically and submitted for clinical assay. Rowntice<sup>4</sup> and others were convinced early that they possess a real therapeutic value. They are now marketed under an approved nomenclature acceptable to the Council

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<sup>\*</sup> Delivered before a Regional Meeting of the American College of Physicians, Denver, Colorado, June 24, 1944.

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Powdered Beef Bone . . . . .	2	Lipid (ether extract) . . . . .	3.0
(Specially prepared for human use)		Gross Fiber . . . . .	0.9
Sodium chloride . . . . .	1	*Including:	
Alkali Leaf . . . . .	1	Calcium . . . . .	0.71%
Dried Flower Yeast . . . . .	1	Phosphorus . . . . .	0.62
Refined Iron . . . . .		Iron . . . . .	0.03
(11 Gm per 100 Pbl)		Copper . . . . .	0.0013

Approximate 10% Calorie per oz or 3.7 per Gm. 12 level tablespoonsful = 1 oz.  
Lactose content is less than 1.0 per 100 grains within 100 grains. 100 grains (virtually 100%)

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of Pharmacy and Chemistry of the American Medical Association<sup>5</sup> as follows

“Adrenal Cortex Extract, Upjohn  
Adrenal Cortex Extract, Wilson Laboratories  
Cortin, Roche-Organon  
Eschatin, Parke-Davis”

It is specified by the Council that as evidence of their standard of strength 1 c c of the solution represents the extract derived from 40 grams of fresh gland. That and that alone is the evidence of their potency.

There is no doubt that these extracts contain the hormone or hormones that are necessary for life. Nor is there doubt that, when given in adequate amounts and at adequate intervals of frequency, they have the power to prolong the life of patients suffering from uncomplicated Addison's disease and to cure the crises arising from complications. Besides, they have the merit of being *safe* products and can, therefore, be used by any physician under any ordinary circumstance of practice. No bona fide case of overdosage has ever been recorded.

However, they have some clinical drawbacks. For instance, their potency has not been proved to be constant. This is not unexpected for, as Thorn<sup>6</sup> points out, their activity depends both qualitatively and quantitatively upon the presence of a number of steroid compounds (15 or 20 have been recovered from the suprarenal cortex) and the relative amounts of each steroid compound in a given batch of the extract. Since the only guarantee of potency is that 1 c c of the extract represents 40 grams of fresh gland, the clinical results are not always predictable.

Then, when used in adequate dosage, the cost alone is often prohibitive. An adequate total daily dose rarely falls below 10 c c, and such amounts of extract usually retail at about \$5.00. A daily total dose of 20 c c not uncommonly is needed to preserve a normal condition. Even more than 20 c c is sometimes necessary as a daily maintenance dose. Such amounts at such prices often fix the hormone cost alone at \$1,500 to \$5,000 per year. Obviously such costs are beyond the reach of the average patient.

Finally, and least objectionable, is the inconvenience and pain incident to the intramuscular injection of 5 or 10 c c at one time, and that amount repeated once or twice in 24 hours. This objection may be circumvented in part by having the assistance of an attendant and by the addition of 0.5 c c

clinical use But the search has been attended by a much better understanding of the different types of metabolic defects of the Addison syndrome, and in a measure, has determined just what specific steroid corrects each particular and specific defect of this deficiency disease of the suprarenal cortex

Certainly the most obvious and measurable defects of suprarenal insufficiency are, first, a loss of normal control of pigment deposit in the skin, second, a loss of the normal regulation of the carbohydrate metabolism, and third, a loss of the normal power of retaining the blood electrolytes The first is unimportant, its basic cause is unknown, and the specific correcting steroid is as yet undiscovered However, the defect of carbohydrate regulation and that of maintaining normal electrolyte blood levels are exceedingly important defects, and each may be effectively controlled by a specific steroid compound<sup>8</sup> Since control of the electrolyte levels in case of Addison's disease is attended by such desirable clinical results as subsidence of gastrointestinal irritability, restoration of feeling of well being, gain in weight and strength and in the normal vascular tension, and since this control of the electrolyte level is brought about quickly and effectively by and only by the steroid desoxycorticosterone (Loeb<sup>9</sup> and Kendall<sup>10</sup>), it has been chosen as the crystalline steroid compound of choice for use in replacement therapy Although these desirable clinical results are attainable by the use of desoxycorticosterone alone, it in no way corrects the defect in carbohydrate regulation,<sup>10</sup> and consequently lacks the ability to prevent a single symptom stemming therefrom Fortunately, the consequences of this defect are not usually as grave as are those of electrolyte control In passing, we call attention to the recent conclusion of Thorn<sup>6</sup> that, since Reichstein is now able to synthesize steroids with an oxygen atom on the C<sub>11</sub> position, it ought not be long before corticosterone (a weak sugar and electrolyte controlling hormone) and hydroxycorticosterone (a strong sugar controlling hormone) are brought into clinical use, much as synthetic desoxycorticosterone (a strong electrolyte controlling hormone) is now employed

Desoxycorticosterone was synthesized by Reichstein and Steiger<sup>11</sup> in 1937, and the following year Reichstein extracted the identical hormone from cortical tissue Only the synthetic product has become available for clinical use Because of its rapid absorbability it is marketed as an acetate ester, thus prolonging its period of activity Delayed absorption is further enhanced by dissolving the steroid compound in an oil, such as sesame or some other inert substance This type of preparation has been devised for intramuscular injections because the steroid compound is impotent when taken by mouth and only weakly potent when administered sublingually Three products have been listed as acceptable by the Council on Pharmacy and Chemistry<sup>8</sup> and are marketed under the trade names of percorin, dyacortate Each product contains exactly 5 milligrams of the steroid compound per 1 cc. of oily solution and of course possesses equal potency Unlike cortical extracts, they are absolutely interchangeable



Percortin is also marketed in sterile pellets 125 milligrams in size. They are intended to be used as subcutaneous implants. The main reasons for preparing a product for this type of therapeutic procedure is to obviate the necessity of daily hypodermic injections. Hormones in oil require a strong needle of larger bore than is used for aqueous solutions. There is more difficulty in filling and emptying the syringe, and there is always some pain attending the process. Also, it is not yet proved that a daily injection of an inert substance having the bulk of 0.5 to 1.5 cc. is wholly an indifferent matter. Besides, the cost may be reduced almost half by substituting implantation of pellets for hypodermic injections. Then, too, despite esterification and oily solutions the delivery of the hormone is not constant throughout the 24 hours between injections. Finally, implantations are required only about once a year, whereas the hypodermic injection is a daily chore for life.

Before implantation is considered, the doctor and patient should be reconciled to spend two or three months in an attempt to determine as accurately as possible the daily hormone requirement of that particular patient. The daily dosage of the steroid compound is accomplished much as is the insulin dosage in case of diabetes. In both cases, it is a sort of clinical titration, a backing and filling method, differing only in the type of criteria which have come to be recognized as end points indicating adequate dosage.

The following is a satisfactory procedure for determining the daily hormonal requirement. First, give the patient 3 to 6 grams of salt each day. We prefer 3 grams. This may be given in the form of 1 gram enteric sodium chloride with each meal. Some prefer giving the salt in a flavored aqueous solution.<sup>7</sup> The important thing is that a fixed and adequate amount of sodium chloride be given from day to day. Such a procedure will reduce the daily requirement of the hormone and will give a more elastic and adjustable program. Then begin by giving a daily subcutaneous injection of 1 c.c. of the oily solution (5 milligrams of the steroid compound). The patient should be carefully examined each day, the physician taking particular note of increase in weight, vascular tension and pitting edema of the shins. Should there occur a rapid increase in weight or pitting edema, the daily dose should be reduced by half, but the daily injections continued. By trial and error, the appropriate dose may thus be determined which will give to the patient a feeling of well being, and his weight, strength and

Assuming that a satisfactory clinical endpoint has been attained by giving a daily injection of 1 c.c. (5 milligrams of the hormone) and no untoward signs or symptoms have appeared in eight weeks, the patient, we think, is then ready for pellet implantation.

It has been determined by animal experimentation and clinical use that one pellet of desoxycorticosterone acetate, weighing 125 milligrams, when implanted under the skin, gives off to the implanted individual approximately 5 milligram of the hormone in 24 hours. If the patient's daily dosage requirement has been determined to be 5 milligrams of the steroid compound, then it will require the implantation of 10 pellets to meet adequately his daily hormonal needs. In our limited experience, we have found this procedure of standardization, as well as the indicated pellet implantation, relatively safe. In uncomplicated cases of Addison's disease, it gives normal electrolyte levels in the blood and corrects the important signs and symptoms arising from the single Addisonian defect of electrolyte control. Theoretically, such implantation should be effective for approximately 250 days. Practically, they may effect adequate control for 10 to 15 months.

The technic of implantation as developed by Thorn and associates is as follows: "The infrascapular region in the mid-clavicular or posterior axillary line is a convenient site for the implantation of pellets. Observation of strict asepsis is absolutely essential. Under local anesthesia a transverse incision 2.5-5.0 cm. is made. The pellets are implanted in the subcutaneous tissues preferably at a distance of at least 1.5-2.0 cm. from the site of the incision. With blunt dissection a small 'pocket' may be prepared for each pellet, the implantation of the pellet being facilitated by inserting the pellet through a small nasal speculum. Employing this technic it is possible to insert as many as 10-15 pellets through a single incision, 2.5-5.0 cm. in length."

As a further precaution against infection, it is advised that the pellets be passed through ether just before implanting. Also, great care is urged in handling the friable tablets with metal forceps in order that they may escape a crushing grasp and thus preserve the calculated daily rate of pellet absorption. Also when "dropped" into the subcutaneous pockets, care should be exercised to plant them 1.5 to 2 centimeters away from the line of incision, thus guarding against pellet extrusion.

Other techniques for the implanting of crystalline hormone pellets, not only for desoxycorticosterone acetate but also for the estrogens<sup>12</sup> and testosterone propionate,<sup>13</sup> have been devised. Special attention should be called to the recently developed technic of De Muro<sup>14</sup> who suggests implantation by means of a small trocar and glass rod obturator. This reduces the length of the skin incision and so simplifies the implantation technic that it is fair to become a simple office or at least dressing room procedure.

Although pellet implantation is a moderately satisfactory and perhaps the best method for treating uncomplicated Addison's disease at this time, it has no place in the treatment of crises of adrenal insufficiency, whatever the

cause The common crises are those arising from neglect in treatment, the complications of intercurrent infections, surgery or accidents, overheating, or the administration of thyroid hormone Adrenal crises may also occur in otherwise normal patients who have had bilateral adrenalectomy, or bilateral hemorrhage into the suprarenal cortex (Waterhouse-Friderichsen syndrome) These complications are still best treated by rest, intravenous sodium chloride solution, cortical adrenal extract, desoxycorticosterone acetate in oil,—all in quantities relatively massive as compared to the maintenance or standardizing doses previously recommended

Also, it is obvious that pellet implantation is an inappropriate method for administering desoxycorticosterone acetate as a therapeutic test in borderline cases However, when given in oil by daily hypodermic injections, the diagnostic use of the synthetic hormone is one of the cheapest and often most conclusive diagnostic procedures Neutasthenics and chronically nervously exhausted patients are not impressively improved and do not show decisive weight gain Addisonian patients do Since 100 per cent diagnosis must always precede any thought of pellet implantation, it seems appropriate at this point to divert to a sort of thumbnail outline of diagnostic procedures

- 1 Roentgen-ray of the suprarenal glands, when done by special and careful technique, will often reveal some degree of calcification in the suprarenal region Since it may show marked calcification in patients showing only mild evidence of insufficiency, and none in many with gravest insufficiency, it can only be considered a presumptive test Roentgenographic evidence of active or healed pulmonary tuberculosis has a similar value Demonstration of a small heart is also of presumptive value

- 2 Low fasting blood sugars and "flat" glucose tolerance curves are merely suggestive.

- 3 The Cutler-Wilder test, the concentration of the chloride in the urine when a diet poor in sodium chloride and rich in potassium is given for 54 hours, is an excellent test to be used when other methods have failed in borderline cases, but it is too drastic to be used as a routine procedure

- 4 The Kepler-Power water test<sup>11</sup> is a safe and useful routine test

- 5 The reduction in output of 17-ketosteroid excretion in the urine has a presumptive diagnostic value, but the determination of this steroid is

wise to caution that 3 to 6 grams of supplemental sodium chloride in 24 hours is desirable in all methods of treatment, but excessive doses either per os or intravenously is not advised. In at least two cases under our observation, disabling tendon contractures have occurred, and although the administration of excessive sodium chloride has not been proved to be the cause competent critics have thought it possible.

The value of restriction of potassium in the diet has also been soundly advocated. Whereas this precaution is based upon the tendency of potassium to increase in adrenal insufficiency disease and fall with the injection of the crystalline hormone it is questionable whether meticulous attention to its daily intake in the diet is justified. The daily weighing or measuring of foods, and the special cooking procedure that has been recommended are no small items of concern to a patient otherwise handicapped. Besides when used in the presence of crystalline hormone therapy there is a possibility of symptoms arising from low potassium in the blood. Perhaps a warning to patients to avoid foods known to be rich in potassium is adequate precaution in most cases.

#### SUMMARY

1 Replacement therapy was forecast by the first clinicopathological reports of Thomas Addison.

2 Adrenal cortex extracts were the first effective replacement therapy for Addison's disease. They have their limitations.

3 Pure steroid hormones were isolated from the cortex and desoxycorticosterone has been synthesized and, therefore, produced in such quantity at such cost that it has come into practical clinical use.

4 The use of desoxycorticosterone has led to a better understanding of the function of the suprarenal cortex and to the recognition of its limitation in correcting the defects occurring in Addison's disease. Despite this limitation, it is now the agent of choice in replacement therapy.

5 In uncomplicated cases it is best given by pellet implantation.

6 The procedure of choice for implantation is as follows:

- a Establish a diagnosis of adrenal cortex insufficiency.
- b Give from 3 to 6 grams of sodium chloride daily.
- c Advise against the use of foods rich in potassium.
- d If patient is not able to carry on in his usual occupation begin daily injection of desoxycorticosterone acetate until the adequate daily dosage is determined. Continue the sodium chloride treatment.
- e Within two or three months, implant just enough pellets to meet the patient's calculated need. Continue the sodium chloride and to be change the dose when the symptoms so indicate.
- f Redetermine the patient's daily hormone requirements and re-implant pellets about once a year.

- g* Meet such symptoms as may eventuate from the recognized failure to correct the defect of regulating carbohydrate metabolism by appropriate dietary supervision and supplemental adrenal extract injections
- h* Meet the complication of crises by supplemental sodium chloride, adrenal extract and additional synthetic hormone
- i* Encourage the patient by assuring him that a better crystalline hormone compound is in the offing

### ILLUSTRATIVE CASES

*Case 1* E. H., female, age 37, two years previously had begun to lose weight and strength. Bouts of vomiting occurred once or twice a month. The condition was regarded as an exhaustion syndrome. Pigmentation began one year previously. February 14, 1944, because of vomiting, exhaustion and loss of consciousness, she was hospitalized and treated for run down condition. May 6, 1944 she came to Colorado General Hospital having "awful black color," weakness and nausea. She was given NaCl, 1 gram t.i.d., plus 2 mg. desoxycorticosterone acetate. Blood pressure ranged from a mean of about 85 mm. Hg systolic and 60 mm. diastolic to about 100 mm. systolic and 65 mm. diastolic, and she gained 10 pounds in weight. There was no skin edema. She felt well. She thought that her skin was "much lighter." Optimal dosage of hormone had not been determined. She had slight fever after admission to the hospital, but roentgenograms did not demonstrate pulmonary tuberculosis. The Cutler-Wilder test, roentgenograms of the suprarenals, and therapeutic test were positive. She showed the classic signs and symptoms of Addison's disease. The dosage was to be further standardized and implantations made after about two months.

*Case 2* J. C., male, age 16, in 1942 complained of exhaustion. The diagnosis was made by Dr. V. T. Austin of Urbana, Illinois, Addison's disease being suspected because a teleroentgenogram revealed a disproportionately small heart. Typical Addisonian crisis occurred with a blood pressure of 55 mm. Hg systolic and 45 mm. diastolic and blood urea of 48 mg. He was treated with intravenous salt and desoxycorticosterone acetate hypodermically. The patient developed anasarca. Dosage was reduced and he came to us in fair condition on 7.5 mg. every third day plus 4 grams of salt daily. During February and March of 1943 we determined his optimal hormonal daily dose to be 6 mg. plus 3 grams of salt. Therefore, 12 pellets were implanted on March 29, 1943. Subsequent rise of blood pressure to 150 mm. Hg systolic and 100 mm. diastolic called for salt withdrawal. After 15 months and without any other medication, his blood pressure was 110 mm. Hg systolic and 70

August 25, 1941, so salt was reduced, then discontinued. He carried on as a farm hand, but by December 24, 1942 he was reimplanted with eight pellets. He was about to return for third implantation.

*Case 4* E. L., female, age 52, in 1935 began to feel tired and had spells of nausea. Her friends remarked that she was becoming brown and very dark by 1939. On October 10, 1939 Dr. Mathews of New Orleans diagnosed her condition as Addison's disease and referred her to Dr. Thorn of Johns Hopkins Hospital for treatment. The optimal dosage was determined and eight pellets were implanted June 22, 1940. In 1940 she was under our care during the summer. She was very pigmented, feeling fairly well, but with a systolic blood pressure of 180 mm Hg. In the autumn Dr. Thorn had some of the pellets removed. February 15, 1942 she was reimplanted with four pellets. She returned to Colorado General Hospital in June 1943 and we implanted two pellets. August 24, 1943 blood pressure was 130 mm Hg systolic and 90 mm diastolic and she was feeling well.

Complication: Tendon contractions occurred in November 1940. Also, when she exercised she had hypoglycemic reactions which were controlled by a Seale Harris diet. She was able to work, save for tendon contractions.

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## PERSPECTIVES OF PSYCHIATRY

By WILLIAM C MENNINGER, Colonel, M C . A U S . F A C P ,  
*Washington, D C*

PSYCHIATRY again stands on the world's doorstep, with the spotlight of the war setting it forth in high relief. Momentarily, as its representative before this group, I should be more literal, indicating that the needs for psychiatry are more acute, more pressing, more widespread than ever before. I am not too confident that psychiatry can rise with sufficient knowledge and strength and tact adequately to meet the challenge. I am confident that if these problems are to be met, if the wider recognition of their existence is to be grasped, the guidance must come through all organized medicine. If solutions are to be effective, it must be physicians—general practitioners, internists, surgeons—who further their development, who envision the many ramifications of psychiatry and who apply its principles and knowledge to these ramifications.

It is not merely a figure of speech to state that we are experiencing a world-wide psychosis. If we are to include in the concept of health, the mental status of an individual, never in the world's history have we had such an unhealthy state. Just as a widespread serious epidemic of a fatal disease commands the attention of all organized medicine, so should the present advanced mental disease of the world arrest all organized medicine. Furthermore, this state of affairs should not merely arrest our attention but should command our united attack upon the causes, the symptomatology, the treatment, and ultimately the prevention.

the Army, the Surgeon General has placed the Neuropsychiatry Division on an equal level with the Medical and Surgical Divisions

We in this country know almost nothing of the suffering and the misery and the unhappiness, all of which are acute symptoms of mental ill health, that prevail in Poland, in Greece, in China in the prison camps of Japan, in the concentration camps of Germany. Perhaps it is fortunate for our own mental health that we can so inadequately, even speculate as to the vastness of this psychiatric problem. However, we have gone far enough in the participation of the war to recognize that just as in 1917 and 1918, a tremendous impetus will be given to psychiatry. The need for it is acute and extensive, and I am referring here not merely to the need for therapy, as important as that is. It is only one of the problems with major psychiatric implications in a nation at war, and in an Army waging that war. My comments are necessarily greatly colored and largely based on the orientation, a reorientation that I have experienced in the last 18 months in the Army, six of which have been spent in the Surgeon General's Office. As the individual responsible in some degree for the mental health of an Army of our size and the psychiatric policies and practices which prevail in it, I quickly admit having a sense of great humility and a keen awareness of a vast responsibility.

It has been my intention to indicate that we are recognizing the importance of psychiatry as applied to the Army. Censorship prevents my indicating to you in any statistical way the size of this problem. You are familiar, however, with the approximate size of our Army. You are probably familiar with our screening method at the induction centers in which the psychiatric rejections represent a considerable portion of the men eliminated. Of the men who are accepted, we must recognize that they have experienced from 17 to 36 years of a particular type of life in which they have done as they wished, migrated when and if they wished, worked at a job of their own choosing, and within the limits of our civil laws have lived at least 16 hours a day with free choice of their social, emotional and economic activities. The great majority developed a sense of security based on attachment to their home and family, to their job and to their friends. And then, in a majority of instances through no choice of theirs they were brought into the Army and as quickly were separated from these pillars of security and satisfaction that had always surrounded and supported them. In their stead they were regimented and disciplined and exposed to a strenuous existence all of which are necessary elements to any Army. For many soon the majority, these experiences are followed by more rigorous training, further separation, and then a departure for parts unknown, a step the psychological significance of which cannot be minimized. Then there is the period of waiting, probably more training, acclimation to new environments, often difficult climate and terrain, possibly with isolation and monotony. And finally, there is combat, the supreme test of adjustment.



One might summarize this whole picture psychiatrically by indicating that there are no experiences in the average civilian's life demanding such major psychological readjustments. There is no comparable series of events which places so much stress and strain on the adjustment capacity of every individual participating. The incidence of mental illness in civilian life is no small figure. We know that one out of every 22 persons will at some time or another be institutionalized because of mental illness, and this figure only represents the psychoses. We are familiar with the fact that at least 50 per cent of all patients who go to all physicians have functional disorders. We hear often quoted the fact that more than 50 per cent of all our hospital beds are for seriously ill mental patients, and such figures do not take into account the greatest number of personality maladjustments who never go to hospitals, often never go to doctors. They somehow manage to adjust their lives, carry their crosses, and either are not aware that they can seek help or are never under sufficient pressure to so do.

With these facts in mind regarding needs in our civilian population and then the picture of the stresses and strains in the Army, it is not surprising to discover or difficult to estimate the size of the psychiatric problem in the Army. Although our screening process at the induction centers eliminates a fair percentage of the large group of maladjusted individuals, even the casual visitor at a consultation service in a replacement training center, a regimental dispensary, is impressed with the opportunity, the need for psychiatry. Even more pressing, perhaps more surprising, is the experience of making rounds on the cardiovascular ward or the gastrointestinal ward or the orthopedic ward of an army hospital. Just as we find in civilian life, a fair percentage of the patients in these general medical and surgical wards are fundamentally maladjustment problems, with their emotions expressing themselves in their heart, their stomach, or their back. Many non-psychiatric critical observers have reported their keen awareness for the great need, not only of psychiatrists, but of a psychiatric understanding and foundation for every medical officer.

My title was "Perspectives of Psychiatry." The perspective of any picture depends on two fundamental factors: first, one's background of the subject matter, and second, his relative position in relation to the picture. Regarding the first point, the background of appreciation, reference was made above to the status of psychiatry prior to the last war, and its much wider recognition following that war. That psychiatry is still far too widely regarded as a highly specialized field concerning itself with an isolated group of patients, patients usually isolated from all other groups of sick people. Through the heroic efforts of some of our leaders, medical schools are teaching far more psychiatry than they did 20 years ago, but the fact remains that most of our students still leave medical school with no conception whatever of the anatomy of the personality or the physiology of the personality. The average physician in the study of his patient far too often makes no inclusion of the study of the individual's personality, even though

he may with meticulous care study the chemistry and physical pathology. One must conclude that even with the great advances of medicine and the equally great advances of psychiatry, the latter is still only vaguely appreciated in its universality and the applicability in general medicine. We must admit of the scotoma that in no field of medicine is there so much obvious observable and yet almost totally ignored pathology in every day life as is seen in the field embraced by psychiatry.

Further evidence is seen in the curious dichotomy which has separated psychiatry from public health. A few of our more progressive states have Mental Hygiene Commissions, but these are pretty largely concerned with the administration and the social legislation connected with the state psychiatric institutions. Rarely is psychiatry included in the field of preventive medicine, which is another admission of our failure to recognize the widespread prevalence of mental ill health and the comparatively simple measures which might be utilized in its prevention.

It has long been my contention that the blind spots involving this subject are in part the fault of psychiatry, and more particularly the psychiatrists themselves. Far too long have they been inclined to an isolationism. Too many times their presentation before non-psychiatric audiences have been too involved, too technical, sometimes verging on the mystical. The group as a whole has been guilty of withdrawing, and in many instances even losing contact with the progress of medicine in general. Fortunately, these failures of the past are being recognized, and I can assure you that many of us are making strenuous efforts toward their correction.

If we conceive psychiatry as the special field of medicine concerned with the thinking and the feeling and the behavior of a man, and particularly those deviations which make him ineffective or a threat to our social system of living, then we should recognize that the fundamental principles in this field should be a basic medical science and not confined to a specialty. And now the war, like a cloudburst, has fallen upon us, and malignant psychopathology is evident on all sides. The suffering and the pain, yes, and the mortality, will be greater than the combined effects of the 10 greatest epidemics that the world has ever known. Nor does one have to go to the psychopathy of Germany or to the tragedy of Greece, Poland, Belgium and Denmark. One sees the direct results of the stresses and strains within our own Armed Forces. One can see it in the firesides of our own civilian life.

All this leads to my second point regarding the perspective of a particular picture, namely the relative position in which one stands. In my own position, my subjective feeling is that I am standing in a valley, surrounded by mountains, mountains each of which presents challenges to be climbed. In fact, I feel they *must* be climbed, and climbed immediately. Each represents an opportunity, a necessity of a particular job that is included in my vista, and the acuteness of the situation and the pressure of time make immediate action imperative. May I describe some of these mountains not only because of your interest in psychiatry and its application in the Army

but because in almost every instance there are far reaching implications which apply to our civilian situation, both present and future

The first mountain in my perspective of psychiatry as it is practiced in the Army is its intimate relationship to the other fields of medicine, particularly internal medicine and surgery. Much more so than in any civilian situation, our physicians in the military forces work in groups and with a closer liaison between the various specialties than prevails in the civilian hospitals or clinics. There are many factors which lead to this close working relationship. A soldier with any type of disability which prevents his full functioning in the field becomes a hospital patient. We do have dispensaries for very minor difficulties, but the soldier is subject to a rule of all duty or no duty. He is either entirely on the job or he is in the hospital, there is no intermediary for even temporary disposition. The result is that we see many more functional complaints than appear in the civilian hospital. An immediate result of this fact is a very free usage of a consultation system between all departments within the hospital. Perhaps the lack of competition between the medical confreres facilitates this system. No one need fear losing his patient to the consultant. The fact that there is no monetary factor is also a strong influence toward the frequent usage of consultations. Regardless of causes, the total result is a very close relationship between the internist, the surgeon and the psychiatrist. There is no doubt that this system makes it possible for the psychiatrist to maintain a much closer relationship to the general progress of medicine and surgery than he ordinarily does in civilian life. It is equally true that the internist and surgeon have a much closer contact with psychiatric problems and treatment than the civilian hospital permits. In many Army hospitals, all cases for elective surgery have a pre-operative psychiatric consultation. It is to be expected that all fields of medicine will benefit by this closer relationship, and it portends the possibility of a much wider utilization of psychiatry, and also the group practice method of medicine which encourages such.

A second mountain in my perspective of psychiatry, based on our experience in the Army, is the importance of the group welfare in contrast to the importance of the individual. The practice of medicine is pretty largely developed on the basis that the individual is the all important unit, and in our private practice of medicine, including psychiatry, our interest and concentration have been on the individual, his needs and his problems, his symptoms and his treatment.

In the Army, we have of necessity focused our attention, particularly in psychiatry, on the welfare of the group. Our management of a particular individual is many times entirely guided by our concern and interest in the group. In fact, I suspect that in some instances, those of us in the practice of psychiatry in the Army have had to alter certain of our principles which we believed in and practiced in civilian life.

Specifically, we have situations in which to some degree the attention to and consideration for the individual has to be sacrificed, perhaps more lit-

erally compromised. Thus we may find an individual who is fundamentally a neurotic person, who capitalizes with a considerable amount of conscious intent on his psychoneurotic ailment. In the Army he is sometimes called a "gold-brick." The fact that he constantly capitalizes on these symptoms makes him no less a neurotic, but this conscious exaggeration of his symptoms is recognized by his fellow soldiers, by his officers and by medical officers. Sometimes they are unsympathetic with him and his behavior is a liability to the group morale. In civilian life we could spend time and effort in an attempt to change him, as well as to manipulate his environment in so far as it might be possible. In most instances we can do neither effectively in the Army and often have to meet this problem by disciplinary measures. Another example is observed in the rather frequent experience of a type of individual who is assigned to overseas activities. He reaches the port of embarkation, but somehow or other manages to miss his train to miss his boat. According to his story it is always an unhappy accident, but everyone else appreciates that it is a very fortuitous accident. Many such individuals merely need reassurance for their "gang plank jitters", others are undoubtedly what we would term, in psychiatric parlance, neurotic characters. In the Army nomenclature, they are termed constitutional psychopaths. Our best management in the majority of such instances is the application of disciplinary measures and not psychiatric therapy. If we treated either of these types of problems with our civilian psychiatric methods (even if the manpower situation permitted) where the individual was paramount, the whole unit would suffer an acute drop in its morale and in its confidence in its officers because even the most stupid individual can see the conscious purpose of the soldier in such behavior.

Furthermore in the Army, regardless of whether it is an antitank squad, whether it is an infantry platoon, whether it is a team in a B17, in all instances they are a team. They must work as a group, and their efficiency depends upon the cooperative efforts of every man in the group. As a consequence, throughout the Army the group becomes paramount and the individual, in some degree, loses his identity.

In the practice of medicine in the Army, we must follow this lead and consider first the welfare of the group rather than that of the individual. This principle has certain implications in civilian medicine. It may be at least in as far as psychiatry is concerned that our great investment of interest and attention to individuals has tended to make us lose interest in the group. In the Army, chiefly because of our shortage of manpower, our psychiatric therapy is planned and administered on a group basis. Our psychotherapeutic sessions, the activities involving occupation, recreation, education, are almost entirely given on a group basis rather than on an individual basis. As a result we are learning many things about how we can manipulate a group, its attitude, its motivation, its behavior. We are bringing various therapeutic influences which one member within the group may have upon other members of the group and conversely the other members

the group of opinions and attitudes on an individual member. In view of our acute shortage of psychiatrists in civilian life, the methods and results learned in the Army may greatly influence our civilian practice of psychiatry. This method is not new but its extensive use because of necessity and consequent improvement within the Army may be expected to provide some very valuable experience applicable to civilian practice and needs.

A third mountain of challenge from my present vantage point concerns our evaluation of personality. My immediate and practical concern is the development of the best methods possible to select those recruits whose personalities are most suitable to serve in the Army. In the neuropsychiatric examination in our induction centers we are greatly interested in how we can best accomplish this, so that from the large number of men who pass through these centers daily, we may pick those who are most likely to succeed. Never before have we had so rich an opportunity to study selection methods. Not only are we able to learn of our mistakes subsequently, but much more important, we are able to see how the man works out in the job given him.

From our meager data at hand we are aware, at least at the moment, of many paradoxes—paradoxes that indicate the inadequacy of our knowledge and methods. We know that many men whom we picked for the Armed Forces fail. We know that many whom we learn through closer scrutiny after their acceptance, have had a long history of maladjustment and yet make an unusually enviable record in the Army. Our job is an extremely difficult one. We must attempt to evaluate how an individual is going to withstand the stresses and strains that we know to exist in Army life, in a period which at most averages two or three minutes. Obviously this cannot be adequately accomplished, and yet that is our responsibility and we must accept it. As a result we have developed, and are in a continuous process of further developing, rapid selective methods which will aid us in determining a man's stability, a man's emotional maturity, a man's intellectual capacity, and a man's sense of social responsibility.

The implications from this experience in selection may have, in fact, should have, tremendous value for our civilian life. The most immediate illustration that I could cite is the psychiatric evaluation of our prospective medical students. Very possibly I am wrong, but I know of no medical school that makes any attempt to evaluate psychiatrically its incoming students. It is widely recognized that many of our failures in medical school are due entirely to personality difficulties. In the Army, we have become disconcertingly aware of the fact that an unreasonably large proportion of all Army officers retired because of psychiatric difficulties are medical officers.

This same experience and knowledge which we are gaining from our psychiatric evaluation of soldiers at Induction Centers can apply to many other problems, in addition to the examination of prospective medical students. It undoubtedly can be used effectively in many fields of industry, in

business, and in other professions. Many of the devices that we may be able to perfect, which will aid in the selection of men who can become a success in the field that they choose, will be of inestimable value to that field and the individuals concerned as well as even a greater saving to those who are excluded.

A fourth mountain to be climbed from my valley is the opportunity to study and evaluate the adjustment process under periods of great stress. As has been indicated above, there is probably no civilian situation which presents the necessity for such radical adjustment processes as are demanded within the Army. This applies not only to the immediate training situation when a recruit leaves the security of his home situation and enters the discipline and regimentation and strenuous existence of Army life. Very surely, there is nothing that is comparable to the adjustment necessary by the former civilian when placed in a wet, muddy fox-hole, exposed day after day to shell fire and constant threat to life, with inadequate sleep, nearly impossible physical conditions, and cold K rations day after day.

Many personalities can withstand this sort of thing for a time. We are convinced that a great majority of those who do break under such circumstances could not possibly have been weeded out by any psychiatric or psychological screening device that we now know. Nevertheless, even within that group, there is a differentiation of those who can stand stress for five or six days, others that can stand it for two or three weeks, others that can apparently withstand its strains indefinitely. There is no doubt that every individual is very grossly affected, is probably changed in certain fundamental portions of his personality. It is a rare opportunity to attempt to determine the significance of various factors in the individual's past life experience, his early psychological trauma and the influence in his childhood and adolescent up-bringing as they affect his adjustment capacity. It is to be regretted that, under terrific pressure of war and our shortage of manpower, we do not have research facilities to study such situations in detail. Obviously this is impossible, but I hope we can gather meager bits of information and observation together from many sources and observers to crystallize some findings that will might revolutionize our psychiatric methods, very possibly our psychiatric concepts of what is and is not important in the developmental influences of an individual's life.

With all this opportunity to study the soldiers who can and those who cannot withstand the stress, there is the corollary of an equally important opportunity for us to attempt to find aids and provide assistance to help them adjust. Thus we have become acutely conscious that motivation is an extremely important psychological factor in aiding the individual to achieve his goal. We have learned that if a man's aim, if his desire, if his wish is sufficiently strong, this motivation may influence his adjustment capacity more than any other factor. If the job seems important enough to the individual and if the individual feels that he is important enough to the accomplishment of the job, his adjustment capacities are tremendously

extended We have also learned that when this motivation is weak, when a man does not have any clear conception as to why he is fighting or why he should be in the Army, our morale is low and our NP casualties are in direct proportion to the state of the morale

Another equally important aid in this adjustment capacity is leadership The principle is as old as the gregarious habits of man, and yet with renewed emphasis we again learn that where the leader takes a personal interest in his men, where he takes the pains to know them and their problems, to express his, and through him, the Army's appreciation of the men's efforts, when he establishes confidence in the men and receives their confidence, the adjustment capacity is again extended in an unlimited fashion Equally, the converse is true, that where the leadership is weak, the morale is low and morale is synonymous with the mental health as reflected in the number of neuropsychiatric casualties that occur This situation is clearly recognized as an analogy of the strong and good father contrasted to the weak and bad father in the primitive family constellation

Still another mountainous challenge as seen from my vantage point is the opportunity to study the integration of the personality in its attempt to adjust to these many stresses and strains and its varied expressions of failure More simply, the extent and variation in the psychopathology are unlimited

To the internist and surgeon, perhaps most impressive is the number of individuals whose personality failure is expressed in somatic symptoms The frequency with which an individual reflects his emotional disorder in the mirror of his soma, more specifically in his stomach or his heart or his cephalalgia or his low back pain, is sufficient to challenge the most organically oriented physician There is no limitation, either in numbers or variety, to the study of these individuals What are the factors that lead one man to express his emotional maladjustment in a dysfunction of his gastrointestinal tract and another man under the same stresses to utilize his cardiovascular system? Perhaps it is our system of medical education, perhaps it is our lack of orientation in psychiatry, whatever the cause, too many internists and surgeons are not stimulated to seek the cause or understanding of such human disease In fact, their most common reaction is annoyance (unless the individual is a well paying client and then we are equally likely to be as unscientific) Rarely is this annoyance recognized for what it is, namely a defense for the physician's own ignorance

The psychosomatic symptoms (and this is an unfortunate term in its implication that only certain physical complaints are psychologically influenced and thus fails to indicate that *all* symptoms are psychosomatic), however, are not the only opportunities which we may study to determine the early signs of personality dysfunction Every medical officer in the Army is aware of the frequency of these signs and symptoms, both the psychological and somatic Their relationship to the precipitating factors is, in many instances, much more obvious and more directly connected than in any comparable situation in civilian experience

The recognition of these mountains that I have been discussing has come as the result of my good fortune of being in the Army and viewing them from that position. Having been until recently a civilian I also can see how much greater a rôle psychiatry must play in the problems of the civilian. I would like to indicate that this contribution to the country's health cannot possibly be made by the psychiatrists alone, but must be a much more important and integral part of the training and practice of every physician.

If mental health is the concern of medicine and if by mental health we mean happiness, efficiency, and social compatibility, then the principles of psychiatry must apply, not only to each of us as individuals, but to our social relationships to each other. The field must be recognized as inseparably linked to the social sciences and concerned with the adjustment and happiness of both individuals and groups. An emphasis must be placed equally on the preservation of mental health as well as the therapeutics of mental illness. We must include in our horizon the methods by which we can obtain a more happy and effective series of human relationships as they apply to family life, to marriage, to education, to economics, to politics, to sociology. We think, for instance, we want a democracy in which we can function as individuals and achieve the personal satisfaction and security of a full and healthy life for every person. We presumably fight for this liberty and freedom and equality, and yet within our own country harbor one of the greatest racial problems existing in the world today. We have paradoxes in our own practice of medicine. We must face the fact that, idealistic as we physicians think we are, we know the problem of medical care for the indigent is far from solved.

Perhaps you may feel that I am going far afield from my subject of the perspectives of psychiatry. You may ask what have marriage and economics and politics and interracial strife to do with psychiatry? You may say they are social problems. It is true they have nothing to do with blood chemistry or surgical technics, but they do vitally concern man's happiness and unhappiness, his motives and emotions. And these are his mental life and his mental health or ill health. They are directly related to medicine and must become a vital concern to medicine.

I do not mean to imply that psychiatry has the answer to any of those questions. I do not think it has, but I feel strongly that it should contribute an opinion, suggestions, a point of view. However, it must yet make great progress in its fund of knowledge and experience and its therapy. If this is ever to be accomplished it must be through its much wider understanding and utilization by every field of medicine.

In closing, may I return to some more immediate and concrete suggestions relative to the more limited field of psychiatry.

*1 Medical Education* Every individual has his rationalized opinion about our medical education, and yet obviously from the ideas that I have presented, it might be concluded and quite correctly so that I feel strongly



that psychiatry should be a basic medical subject. This does not mean that there need not be specialists in the field. There must be. The universality, however, of emotions, of feelings, and their effect on the human body, makes it imperative that every individual practicing medicine be as firmly grounded in the field as he is in physical anatomy, physical physiology and physical pathology.

*2 Public Health* An extension of this same principle should be made to preventive medicine, to public health. Again, if we accept the premise that mental health is a part of medicine, there can be only one logical answer to the necessity of including it in every preventive medicine program. Not only do I specifically refer to the prevention of serious and disabling mental illness, but much more important, the education and extension of our principles of mental hygiene, just as we educate individuals in physical hygiene. It is startling to recognize that there are more deaths from one expression of mental illness—namely, suicide, than there are from the five most communicable diseases. The paradox exists, however, that very few of our public health agencies concern themselves in the least with the mental health of the commonwealth.

*3 Medical Assistants* As medicine becomes more of a social science and involves the assistance of research workers, of laymen assistants, of nurses, and for us in the Army our tremendously important medical administrative corps, we must recognize that these individuals should have a much closer contact in medicine from an earlier period in education than they do. In psychiatry, particularly, is this important, because no psychiatric team, whether it be in an out-patient clinic or in a hospital, can adequately function without the help of the clinical psychologist and the psychiatric social worker. It is to be hoped that some time our medical schools can become universities and include in their training these intimate associates and assistants of the physician.

*4 Reorientation to the Importance of the Personality* In every medical course we start the student in devoting hours, weeks, months, in the dissection of the human body. We follow it with excellent courses in the physiology and the chemistry of this body. We are commendably grounded in the physical pathology of this body. Nonetheless, we suffer in our system of medical education by so much emphasis on the material, that the average medical student receives his diploma with only the vaguest conception that the most important part of his patient is the person who lives within the framework of the body. He leaves with slight, if any, idea that it is our ambitions and our strivings, our loves and our hates, our successes and our failures, our aggressivity and our passivity, that are probably the major determinants in the maintenance of health. From my viewpoint of psychiatry, medical education must reorganize to present an adequate orientation to these facts.

*5 Convalescence* The recovery of every individual from every type of illness is very possibly determined more by his psychological life than any

other factor Through some sort of curious scotoma, the consideration of this factor has been conspicuously absent in most studies of the process of getting well Because it happens regularly, we assume that the operation will heal, the pneumonia will resolve, the decompensated heart will readjust We have vaguely been aware of the fact that the recovery of a gastric ulcer does have a more direct and obvious relationship to the patient's emotional life In general, we have ignored the emotional life in our general medical and surgical patients both before and after our specific treatment For pragmatic reasons in some cases, psychiatric study before emergency medical or surgical treatment is not so important as after such treatment Our lesson learned in the Army as to the importance of conscious motivation and our recognition of unconscious motivation make it obvious that such should be considered in every convalescence The physician who fails to do so is an offender against his patient—as well as against the best practice of medicine

6 *Reorientation to Concepts of Mental Health* No field of medicine battles against such a welter of superstitions and misconceptions regarding its patients and methods as does psychiatry Unfortunately, our greatest lack of understanding and most frequent source of misunderstanding lie in the medical profession itself Again it may be in our system of medical education, it may be in the historical evolution of psychiatry from the period of werewolves and dungeons, it may be in the incomprehensible jargon of some psychiatrists, it may be in part the intangible nature of the subject in contrast to operative technic and stethoscopes or roentgen-rays, it may be the presumed necessity to defend our individual and naïve belief that each of us is a "normal" personality, whatever the causes, the fact remains that the physician's bungling of psychological factors keep thousands of cults thriving Because he is a physician and thus the authoritative source of opinions for the layman, his attitude and understanding of psychiatry can and do color the public attitude And even though progress has been made the public conception is still a blurred picture of disgrace and fear, mysticism and self-exemption Is it too much to hope that the medical profession might take a more forceful initiative to gain enlightenment and disseminate it?

May I express my appreciation for your patience and your attention I hope I may have conveyed clearly my own vistas of the psychiatric mountains to be climbed My most important perspective tells me that they are *our* mountains—they face every organized group concerned with medicine and the changing order Will we climb them?

# CHOLELITHIASIS IN SICKLE CELL ANEMIA<sup>\*</sup>

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## INTRODUCTION

SINCE the first description of sickle cell anemia by Herrick<sup>1</sup> a rather voluminous literature about this disease has accumulated. Though the various clinical and pathological features of this condition have been thoroughly studied, the occurrence of cholelithiasis in sickle cell anemia has received very little attention. Hein, McCalla and Thorne<sup>2</sup> described the case of a young adult negro with sickle cell anemia in whom, on autopsy, stones in a thickened gall-bladder were found. They were able to recognize a similar finding in two other cases recorded in the literature. Campbell,<sup>3</sup> discussing the abdominal symptoms of sickle cell anemia, believed that true biliary colic may occur in this disease, and Schaefer<sup>4</sup> described the presence of gall-stones in a patient with this condition. A review of the literature reveals that biliary calculi are not infrequently recorded in autopsy reports and case histories of sickle cell anemia, but the significance of this finding is usually not recognized. Commonly used textbooks of gall-bladder disease do not mention sickle cell anemia as an etiologic factor in the development of gall-stones in the colored race.

Cholelithiasis in sickle cell anemia appears interesting and important in view of the evaluation of the abdominal symptoms observed in this illness. The occurrence of gall-stones in this disease may also numerically influence the incidence of cholelithiasis in the negro about which there is much controversy.

For these reasons we thought it of interest to report the following cases of sickle cell anemia in which the diagnosis of cholelithiasis was made clinically and roentgenologically and to examine the incidence of cholelithiasis in sickle cell anemia on the basis of autopsy reports recorded in the literature.

## CASE REPORTS

*Case 1* H D S, a 13 year old colored male, was first seen in the out-patient department in 1942 when the diagnosis of sickle cell anemia was made. There was a history of frequent episodes of abdominal pain since the age of four. The pain was localized in the epigastrium and in the left upper abdomen and radiated to the back. These attacks were frequently associated with soreness between the scapulae and over the sternum and with aching in the knees and ankles. The family history disclosed that a younger brother was known to have sickle cell anemia.

Physical examination revealed icterus of the sclerae and pallor of the mucous membranes. The spleen was enlarged and quite firm. A systolic murmur was heard.

<sup>\*</sup> Received for publication April 10, 1944.

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over the apex of the heart. Slight tenderness was elicited over the spine and sternum. There were several small scars noted at the anterior aspects of both legs.

**Laboratory studies.** Numerous red blood cell counts ranged from 2,690,000 to 4,350,000 with hemoglobin values of 9.0 to 10.6 gm. From 55 to 95 per cent sickling was observed within 24 hours. An icterus index was 19 and the serum bilirubin 2.0 mg per cent.



FIG 1 Case 1. Colored male, age 13. Cholecystogram shows normal filling of the gall-bladder and 6 calculi.

**Roentgenological examination.** A film study of the abdomen revealed six mottled stones in the right upper abdomen. The dorsal and lumbar vertebrae showed a rather coarse trabeculation and were somewhat osteoporotic. The vertebral bodies appeared decreased in height and increased in width. The examination of the skull revealed that the bones of the calvarium were thickened owing to widening of the diploë which

had a granular, osteoporotic appearance. The inner and outer tables were thin, and no vertical striation was demonstrated. The gall-bladder filled well in subsequent cholecystograms. The stones were visualized within the gall-bladder shadow and were found to be freely movable. The calculi had a non-opaque center surrounded by several layers of calcium with perpendicular striation (figure 1).

**Comment** In a 13 year old colored male with typical signs of sickle cell anemia, gall-stones were demonstrated. Roentgenologically, the calculi resembled mixed pigment stones. The gall-bladder apparently had normal function. Biliary calculi are unusual in a patient of this age and should draw our attention to the possibility of increased production of bilirubin as a result of a chronic hemolytic process.

**Case 2** C. S., a 24 year old colored female, known to have sickle cell anemia, was admitted to Grady Hospital in January 1944 for treatment of a chronic leg ulcer. Since the age of 13 she had had frequent episodes of mild abdominal pain not associated with nausea and vomiting. The pain began in the umbilical region and radiated to the right upper abdominal quadrant and back. Fatty and greasy foods were well tolerated, but the ingestion of certain vegetables caused abdominal discomfort. The stools had normal color. For the past seven years the patient had suffered from a chronic ulcer on the right leg which had been treated intermittently with conservative methods and skin grafts. During the past four months she had suffered from two attacks of joint pain.

Slight icterus of the sclerae and pallor of the mucous membranes were noted. The lungs revealed no pathologic changes. A systolic murmur was heard over the precordium, but the heart was not enlarged. There were no significant abdominal findings. A sharply circumscribed ulcer, measuring 3 cm in diameter and showing several bleeding points, was seen at the anterolateral aspect of the right lower leg. This ulcer revealed healthy granulation tissue, and its edges were not undermined. Scars were observed on the left lower leg.

The erythrocyte count was 2,560,000 with a hemoglobin content of 8 gm. A blood specimen from the fingertip, after compression of the finger with tourniquet for five minutes, showed about 80 per cent sickling. About 40 per cent sickling of the red blood cells was seen in the counting chamber. A small number of nucleated red blood cells was noted. The serum bilirubin was 6 mg per cent. Numerous pus cells were present in the urine sediment. The Kahn reaction was negative.

A cholecystogram (figure 2) disclosed five faceted calculi, from 3 to 7 mm in diameter, lying within the gall-bladder shadow.

**Comment** A 24 year old patient with mild abdominal pain, chronic leg ulcers, and the blood findings of sickle cell anemia was found to have gall-bladder stones. Clinically, it seems to be difficult to rule out cholelithiasis as the cause of the vague abdominal symptoms.

**Case 3** J. R., a 35 year old colored male, was admitted to Grady Hospital for study in November 1943. In 1929 he was found to have sickle cell anemia, and since that time he had been admitted at various intervals for treatment of leg ulcers and for blood transfusions. During these years the patient frequently had attacks of abdominal pain which were interpreted as "crises" of sickle cell anemia. The pain was localized around the umbilicus and radiated to the lower abdomen and legs, and to the left upper quadrant. This dull aching pain was occasionally associated with nausea, but was not related to meals. The color of the stools was normal.

The sclerae were icteric and the mucous membranes were pale. The heart was enlarged to the left and a harsh systolic murmur was heard over the apex. The liver and spleen were not palpated. Both legs showed scars of healed ulcers.

Since the first admission to the hospital the red blood count had ranged from 1,800,000 to 3,100,000 with hemoglobin values of from 6 to 8 gm. Sickle cell preparations revealed 20 per cent immediate sickling, 75 per cent sickling after 12

hours, and 85 per cent sickling after 24 hours. The serum bilirubin was 3.4 mg per cent and the blood cholesterol was 151 mg per cent.

**Roentgenological examination.** The bones of the calvarium were thickened and showed generalized osteoporosis without evidence of perpendicular striation. The heart revealed marked generalized enlargement with prominence of the pulmonary



FIG 2 Case 2 Colored female, aged 24. Cholecystogram shows 5 calculi and normal filling of the gall-bladder.

trunk. A cholecystogram in 1931 showed no gall-stones, and no filling of the gall-bladder was seen at that time. A film study of the gall-bladder area in 1943 disclosed numerous small faceted calculi which seemed to be localized in a contracted gall-bladder (figure 3). Fluoroscopic and radiographic examination of the gall-bladder after administration of contrast medium revealed full filling. In the upright position the calculi descended into the fundus of the gall-bladder.

**Comment** In a 35 year old colored male with typical symptoms and signs of sickle cell anemia, radio-opaque gall-bladder calculi were demonstrated. A cholecystogram at the age of 23 revealed no filling of the gall-bladder, suggesting that the function of the gall-bladder was impaired at that time. It may be possible to at-



**FIG 3 Case 3** Colored male, age 35. Numerous faceted calculi in contracted gall-bladder.

tribute some but certainly not all of the clinical symptoms of this patient to the presence of cholelithiasis.

**Case 1** K. D., a 38 year old colored female was admitted in January 1944 for the treatment of a chronic leg ulcer. Her past history and family history were non-contributory. She had been perfectly well until six months prior to admission when she injured her right leg. This trauma resulted in the development of a chronic

ulcer which became gradually larger and which had never healed. There was no history of episodes of abdominal pain or typhoid fever.

The mucous membranes were found to be pale, and the sclerae were not icteric. The examination of the heart, lungs, and abdomen did not reveal pathologic changes. An ulcerated area, about 5 cm in diameter, appeared above the right ankle. The ulcer was sharply circumscribed and covered with small bleeding points. No varicose veins were seen. Several scars were noted on the left leg.

The erythrocyte count was 2,050,000 with a white blood count of 14,500 and a hemoglobin content of 6 gm. The tourniquet test revealed 30 to 40 per cent sickling of the red blood cells. The urine showed white blood cells in clumps and was otherwise not remarkable. The serum bilirubin was 0.4 mg per cent.

**Roentgenological examination.** The Graham-Cole studies revealed faint filling of the gall-bladder which showed a smooth outline and normal size. Eight small faceted calculi were demonstrated in the fundus of the gall-bladder. After the fatty meal the gall-bladder revealed satisfactory emptying.

**Comment.** A 38 year old colored female with blood findings of sickle cell anemia developed a chronic leg ulcer after injury. Graham-Cole studies revealed the presence of small faceted calculi in a normal functioning gall-bladder. Remarkable is the absence of abdominal crises and other abdominal symptoms in this patient. Evidently we deal here with a case of silent cholelithiasis.

## DISCUSSION

**Pathogenesis.** Increased destruction of red blood cells is one of the characteristic features of sickle cell anemia. On disintegration of the red blood corpuscles, hemoglobin is liberated and converted into bilirubin. Hyperbilirubinemia in these patients is the result of increased blood destruction. This phenomenon is common to both sickle cell anemia and congenital hemolytic jaundice, in which latter condition Mayo<sup>5</sup> observed the presence of cholelithiasis in two-thirds of a group of patients.

According to Illingworth<sup>6</sup> it is believed that an excess of bilirubin in the bile will favor an aseptic precipitation of pigment in the biliary tracts. We have to assume that, once the nucleus of a gall-stone is formed, secondary factors such as stasis and infection will determine its ultimate chemical composition. In most case reports the calculi were described as multiple, small, greenish-black, soft pigment stones. The calculi in our patients were small, faceted and contained a peripheral layer of calcium.

**Incidence of Cholelithiasis.** The number of autopsy reports of sickle cell anemia, recorded in the literature, is comparatively small.<sup>2, 3, 7a-7</sup> Excluding those cases in which a very incomplete autopsy and clinical description is given or which are reported in the foreign literature not available to us, 44 necropsy reports were studied. In 12 of these cases gall-stones were found on autopsy or removed surgically during the course of the disease. The age and sex of these 44 patients are demonstrated in table 1. From these figures it will be seen that cholelithiasis was not encountered during the first decade. Gall-stones were, however, observed in patients who died during the second decade, and quite common in the third and fourth decades. There were no biliary calculi noted in patients of the age group above 40. Anemia



was not a characteristic feature of these latter cases, and it is very likely that they represented the so-called "sickle cell trait" Eight of these 12 patients in whom cholelithiasis was observed were males

Since sickle cell anemia is a disease almost exclusively observed in the colored race, it may be interesting to compare these figures with statistics which deal with the incidence of gall-stones in the negro in general There seems to be wide divergence of opinion about this subject Mosher,<sup>8</sup> in 1901,

TABLE I

Total Number of Autopsy Cases					Number of Cases with Cholelithiasis			General Incidence of Cholelithiasis in the Negro (Jaffe)	
Age	Male	Female	Sex not given	Total	Male	Female	Total	Male	Female
0-10	6	6		12				0	0
11-20	2	6	1	9	1	1	2	0	0
21-30	8	5		13	4	1	5	0	3 28%
31-40	3	2		5	3	2	5	0 73%	7 5%
41-50	1	2		3				0	12 24%
51-60								1 86%	16 27%
61-70		1		1				4 34%	25 0%
Above 70		1		1				6 66%	20 0%
Total	20	23	1	44	8	4	12	1 04%	10 23%

reported an incidence of 5.5 per cent in the negro and 7.8 per cent in the white These figures contrast sharply to reports by Bloch<sup>9</sup> and Alden<sup>10</sup> who were impressed by the rare occurrence of gall-stones in the Southern negro Jaffe,<sup>11</sup> whose figures are in accord with most North American statistics, could demonstrate in a large series of autopsies that there exists a considerable difference in the incidence of cholelithiasis in the colored and white race In white males gall-stones were found six times as often as in colored males, and in white females 1.7 times as often as in colored females This author considered his autopsy material uniform and concluded that the difference could not be explained on the basis of diet, occupation or mode of living

Jaffe's findings, recording the incidence of cholelithiasis in the colored race, are included in table 1 for comparison From these figures it may be seen that cholelithiasis in the younger age groups is infrequent In these age groups, however, gall-stones are most commonly encountered in sickle cell anemia With the generally lower incidence of gall-stones in the colored race, sickle cell anemia may be a more important etiologic factor in the development of biliary calculi in the negro than is generally appreciated

*Cholelithiasis and Abdominal Crises* Episodes of acute abdominal pain, usually localized in the epigastrium, occur frequently in sickle cell anemia Fever, abdominal tenderness, and leukocytosis during these crises may make it extremely difficult to differentiate such an attack from an acute

abdominal condition. Actually, as the literature reveals, a good number of patients with sickle cell anemia have been operated on for appendicitis, cholecystitis, and ruptured peptic ulcer.

As yet the cause of pain in the abdominal crises has not been satisfactorily explained. Hepatic infarcts,<sup>12</sup> splenic hemorrhages,<sup>13</sup> and nerve root pains due to vertebral changes<sup>14</sup> have been suggested. The occurrence of gall-stones in these patients will, therefore, immediately raise the question as to whether such crises could be explained on the basis of biliary colic. This seems unlikely, in view of the fact that many patients with sickle cell anemia do not develop cholelithiasis. It is also known that patients with sickle cell anemia and cholelithiasis have continued to suffer from abdominal crises after cholecystectomy. On the other hand it is entirely possible that many attacks of acute abdominal pain are not caused by crises but may be attributed to true biliary colic.

### SUMMARY AND CONCLUSIONS

Cholelithiasis is not infrequently observed in patients with sickle cell anemia. Four cases of sickle cell anemia are reported in which gall-stones were demonstrated roentgenologically. A review of the literature reveals cholelithiasis in 12 out of 44 autopsy cases of sickle cell anemia on record. All 12 patients were in the age groups below 40 in which according to statistics cholelithiasis is not frequent.

The occurrence of biliary calculi in the negro is not rare. There is, however, sufficient statistical evidence to indicate that cholelithiasis is less frequently encountered in the colored race than in the white race. Since there is a lower incidence of cholelithiasis in the negro, sickle cell anemia gains relative importance as an etiologic factor in the development of gall-stones in the colored race.

It is not believed that the crises of sickle cell anemia can be explained solely on the basis of biliary colic. However, it seems possible that abdominal symptoms in some of these patients are due to cholelithiasis and associated gall-bladder disease.

The recognition of sickle cell anemia as a cause of acute and chronic abdominal symptoms is important in order to avoid unnecessary operations. The mere presence of biliary calculi in a patient with sickle cell anemia requires careful evaluation of all clinical symptoms before operation is advised, since it is commonly known that this disease increases the risk of surgical procedures.

Therefore, cholelithiasis in the negro, especially in the young negro, always demands search for the presence of sickle cell anemia.

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# STUDIES ON THE PATHOPHYSIOLOGY OF SICKLE CELL DISEASE\*

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THE subject of sickle cell disease has been rather extensively studied with respect to its clinical<sup>1, 2, 3</sup> and pathological<sup>4, 5, 6</sup> aspects. Some work<sup>7, 8, 9</sup> has been done to study the disease in a dynamic physiologic way, especially with reference to the hemolytic mechanisms and the peculiar pathophysiology of the red blood cells so characteristic of this disease. Inferences are drawn from these studies to explain the terminal histology as well as many of the clinical aspects. Our interest has been centered on fairly long term studies of the pigment metabolism as one of the dynamic mechanisms which might lead to a better understanding of some phases of the disease process. The question of relative severity of the disease from patient to patient is easily confused by the protean manifestations of a disease such as this because of incidental involvement of more or less vital organs or tissues. For that reason we have chosen to study patients presenting the common hemolytic syndrome in varying degrees of severity.

## CASE REPORTS

*Case 1* B T, colored female, age 13 years, was admitted to the hospital complaining of pain and swelling of the ankles, elbows, fingers, and a sore throat. There was a history of growing pains beginning three years previously, and lasting for two years. The pains in the joints began six months before admission and occurred in intermittent attacks lasting several days. For the last month she had been in bed continuously. There had been some dyspnea on exertion in the preceding six months.

The eyes were known to have been yellow since early childhood.

The temperature was 99.4° F, pulse 118, blood pressure 98 mm Hg systolic and 70 mm diastolic, weight 67 pounds. She was asthenic in build, 5 feet tall, and moderately undernourished. The sclerae were slightly icteric. The tonsils were large, and the arteries of the neck pulsated visibly. The heart was enlarged to 9.5 cm in the left fifth interspace. The rhythm was regular, the apex thrust forceful. There was a soft systolic murmur at the apex and along the left border of the sternum. The first heart sound was not accentuated. The liver and spleen were not palpable. There was swelling and tenderness with limitation of motion of the fingers, elbows, and ankles. Several small nontender nodules were felt on the posterior aspect of the left elbow.

The red blood cell count was 2.01 million, hemoglobin 7 gm, white blood cells 11,900, with 54 per cent neutrophils, 37 per cent lymphocytes, 6 per cent eosinophils, and 4 per cent monocytes. There was 75 per cent sickling of the red blood cells in a wet preparation in 24 hours. The urine was negative for urobilin and urobilinogen.

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The electrocardiogram showed a PR interval of 12 sec, QRS 08 sec., a rate of 104, and no significant changes from the normal curve

Roentgenographic examination showed the transverse diameter of the heart to be 12.8 cm and that of the chest 23.7 cm, with a prominent pulmonary conus. Roentgenograms of the bones and joints showed a general decalcification, periarticular swelling and effusion into the joints. There was some thickening of the inner table of the skull.

The course in the hospital was marked by a migration and slow subsidence of the joint swelling and pains uninfluenced by salicylate therapy, and a variable degree of low grade fever. A single transfusion of 300 cc of whole blood increased the blood count to 2.32 million per cubic millimeter. It continued to rise to a level of 27 to 28 million where it remained for the duration of the study.

Our studies were begun one month after admission, and revealed a rather constant degree of anemia, a leukocyte count of 10 to 12 thousand, and a constantly elevated bilirubinemia. The urinary excretion of urobilin never exceeded 36 mg per day. The stercobilin excretion, however, showed an interesting cyclic variation over the two months' period of study (figure 1).

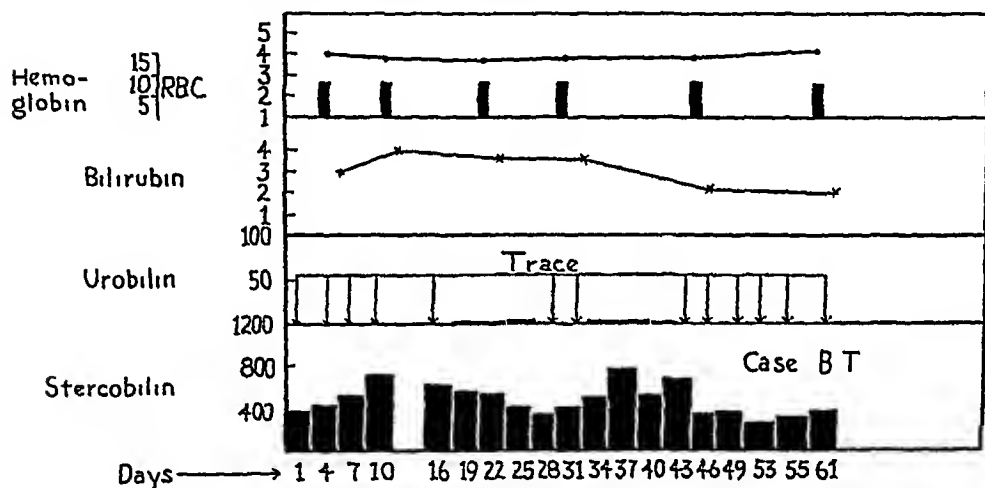


FIG 1

This case is a good example of the moderate degree of anemia associated with signs and symptoms very suggestive of rheumatic fever and carditis. Klinefelter<sup>10</sup> has reviewed the literature and reported 12 cases of his own of this picture of sickle cell disease simulating rheumatic fever. Only detailed study of them suggests that they are not rheumatic in origin, a conclusion not infrequently proved at autopsy.

**Case 2** J McC, a colored male, 13 years of age, was admitted complaining of migratory bone and joint pains of one week's duration. He had developed a toothache in a lower molar a week before the onset of the bone and joint pains. An abscess developed and ruptured through the gum. There were no gastrointestinal or cardiovascular symptoms. He had had frequent sweating since the onset of the present illness. The past and family history were irrelevant.

He was somewhat undernourished, was 4 feet 8 inches tall, and weighed 69 pounds. Temperature was 100.4° F, pulse 90, and blood pressure 90 mm Hg systolic and 70 mm diastolic. There was a definite icterus of the sclerae and swelling and tenderness over the left mandible. The tonsils were enlarged and the anterior cervical nodes and submaxillary nodes were moderately enlarged. The heart was

slightly enlarged, both clinically and on roentgenographic examination. The apex thrust was forceful and there were loud harsh systolic murmurs at all valve areas. The liver was enlarged 4 cm below the costal margin in the midclavicular line. It was not tender. The spleen could not be felt by any maneuver. The extremities were negative.

The red blood cell count was 3.0 million and the hemoglobin 8.5 gm. The white blood cells numbered 21,000, neutrophils 87 per cent, lymphocytes 12 per cent, and monocytes 1 per cent. A wet preparation of the blood showed 75 to 80 per cent sickling in 24 hours. The urine showed 2 plus albumin, but was otherwise negative. The blood bilirubin was 5.0 mg, and the qualitative reaction was positive direct.

The icterus of the sclerae disappeared rapidly. The temperature varied between 99.2° and 100.6° F daily for a week and then subsided to normal.

Our studies were begun on the eleventh hospital day and continued for one month (figure 2). The blood picture at that time showed red blood cells 3.3 million,

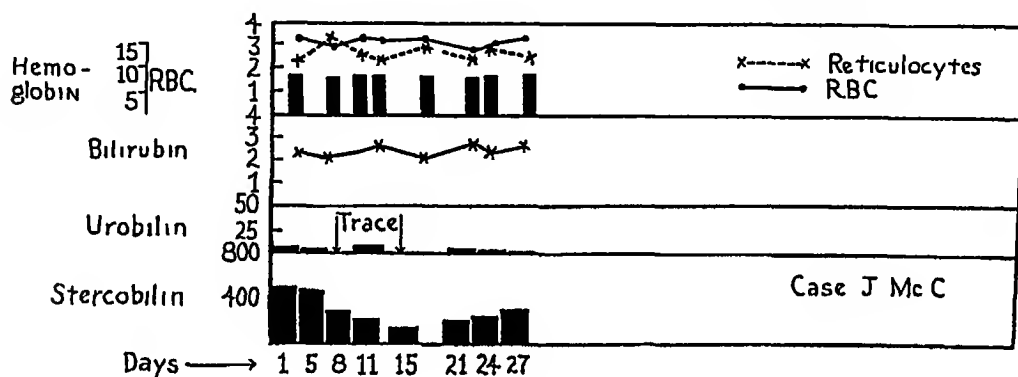


FIG 2

hemoglobin 8.8 gm, white blood cells 17,000, reticulocytes 11.6 per cent, and the blood bilirubin 1.8 mg per cent, with a negative direct qualitative reaction. The intravenous hippuric acid test was normal (74 gm). A punch biopsy of the liver revealed some moderate hemosiderin deposits in the liver cells, slight fatty change, and moderate amounts of glycogen. No erythrophagocytosis was seen.

As can be seen from figure 2, there was little variation in the blood picture or bilirubinemia. The urobilin excretion varied from traces to 6 mg per day. There was a very definite suggestion of a cyclic variation in the stercobilin excretion, as had been observed in case 1. It is obvious that if pigment studies were done at the nadir of the cycle one might consider that hemolysis, as evidenced by stercobilin excretion, was absent. There is further evidence in these two cases that the urobilin is not increased in these milder phases of hemolytic anemia.

The liver gradually receded in size, but was still palpable when he was discharged. Six months after discharge he was seen again. He had been in good health. The liver was not palpable, nor was the spleen. The sclerae were just slightly icteric.

The etiology of the hepatomegaly in this relatively mild case of sickle cell disease is not obvious. In the light of later studies we feel that it developed as a result of active sickle cell disease plus the effects of a suppurative infection, either one of which alone would probably have been ineffective.

**Case 3 M G** (the patient mentioned by Bauer<sup>1</sup>) a colored female, 19 years of age when first studied had a long history of recurrent leg ulcers beginning when she was about 13 years of age at which time she had had an ulcer of the left anterior lower leg which took five to six months to heal. When seen again in 1937 she had an ulcer of four months' duration behind the internal malleolus on the left ankle.

From that time on she had repeated recurrences of the ulceration in this site, and her red blood cell count had varied from a low of 750,000 to 4.42 million, usually running between 2.0 and 2.4 million. A week before the present admission she had noticed a sticking sensation in the left leg in the scar of the ulcer which had been completely healed for five months. It had not been traumatized. The scar broke down and formed a semilunar ulcer.

The patient was a well developed slender colored female. The temperature was 101° F., pulse 88 per minute, blood pressure 120 mm Hg systolic and 78 mm diastolic. The sclerae were lemon yellow in color. The mucous membranes were pale. The

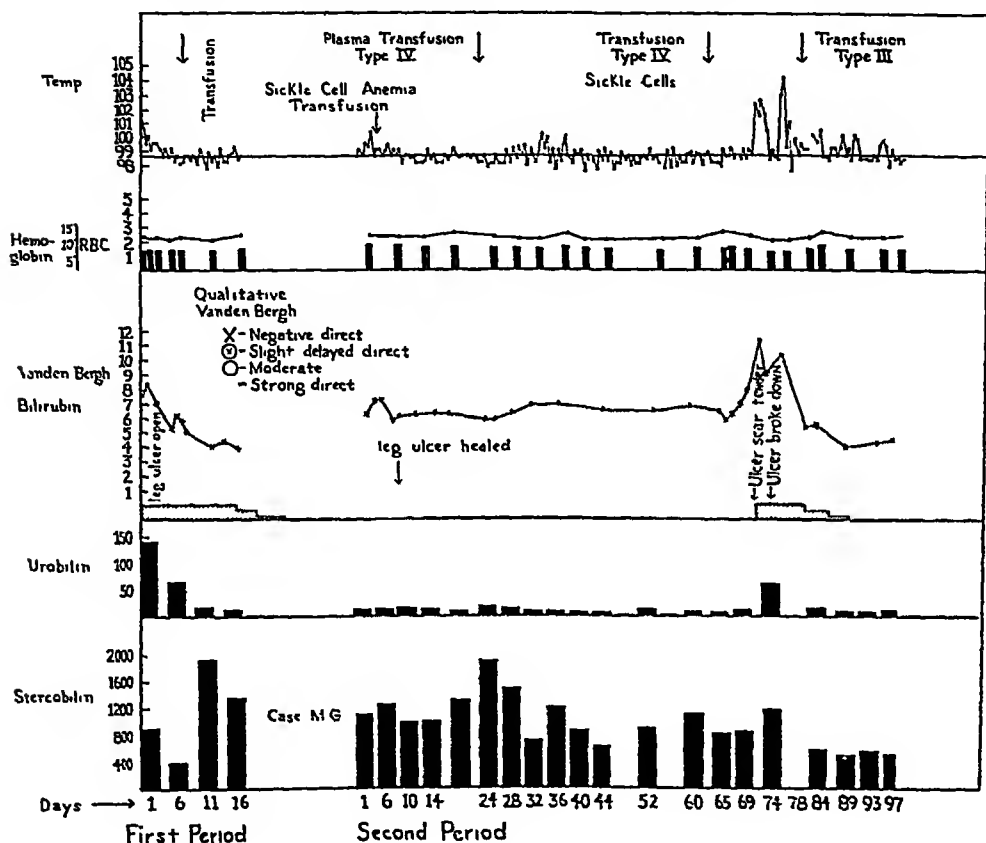


FIG 3

heart was not definitely enlarged clinically. The apex thrust was forceful. The liver was palpable and tender 3 cm below the costal margin in the midclavicular line. The spleen was not palpable by any maneuver. There was an ulcer on the left ankle behind the internal malleolus 1.5 by .75 inches, shallow and indurated, and the skin was hyperpigmented about it. It was tender about the margins.

Electrocardiogram showed a PR interval of 14 sec., QRS 09. The T-waves were low in the first lead. Roentgenographic examination of the long bones and skull showed no changes.

The data from our studies (figure 3) were obtained beginning four days after the patient's admission while the temperature was subsiding. The red blood cell count was 2.4 million, hemoglobin 8.0 gm, white blood cells 9,000, neutrophils 76 per cent,



lymphocytes 16 per cent, monocytes 6 per cent, eosinophiles 2 per cent. A wet preparation showed 100 per cent sickling in 24 hours. The blood bilirubin level was 7.2 to 8.0 mg per cent with a positive direct qualitative reaction. This rapidly decreased to 3.6 to 4.0 mg per cent with a negative direct reaction. The urobilin excretion was excessively high beginning at 135 mg per day and rapidly decreasing to 10 mg per day when the study terminated. The stercobilin excretion followed a very irregular course, possibly influenced by a transfusion of sickle cell blood which was given at the low point of the stercobilin excretion.

The leg ulcer healed nicely in about three weeks' time.

She was readmitted one month later for check-up and was asymptomatic. The leg ulcer was still healed. The red blood cell count was 2.45 million, hemoglobin 8.0 gm, the blood bilirubin 4.8 mg per cent negative direct. She was given 500 cc of whole blood and the red blood cell count rose to 2.72 million, hemoglobin 9.0 gm. During this period, not shown in figure 3, the urobilin excretion varied from 8 to 12 mg and the stercobilin from 500 to 1,300 mg per day.

Second period of study. Two months later she was readmitted with the history that three weeks previously the scar on the left ankle had again broken down to form an ulcer. The red blood cell count was 2.36 million, hemoglobin 8.0 gm, and the white blood cells numbered 15,500. When we first saw the patient on this admission the leg ulcer was practically healed and she was asymptomatic. We continued our studies (figure 3) to observe the effects of transfusions of whole blood and plasma from active and inactive sickle cell disease. We were unable to be certain that any effect was obtained on the hemolytic process.

One week following a transfusion with 275 cc packed red cells suspended in saline from an inactive sickle cell patient, our patient developed a headache and began to run some fever. The ulcer scar became tender and broke down to form an ulcer. The temperature subsided and then rose again to 104° F. She lost her appetite, had some nausea and vomiting, some crampy abdominal pains, and a few loose bowel movements. The sclerae rapidly became deeply icteric, and the liver became tender and enlarged to 3 to 4 cm below the costal margin. These symptoms and signs subsided with relative rapidity over a period of about five days. The leg ulcer then began to heal, and closed over in about two and a half weeks from the initial breakdown.

Besides the febrile clinical course with symptoms and signs of liver involvement during these two episodes, there was a sharp increase of urobilin excretion at the height of the symptoms and signs, the bilirubinemia increased sharply, and the qualitative reaction changed from negative direct through delayed to immediately positive direct reaction. This also subsided rapidly and the qualitative reaction reversed again. Since these studies, we have observed this same sequence of events during two other subsequent periods in this patient.

*Case 4* P. T., a colored male, 16 years of age, was first seen in Charity Hospital in January 1939, at which time he was found to have a liver extending to the umbilicus. The spleen was not palpable. He had open leg ulcers bilaterally which had recurred intermittently over the previous seven years. Nine days before this admission his aunt had noticed that his eyes were getting very yellow. On admission the icterus index was 30 units, the red blood cell count was 2.2 million, white blood cells numbered 16,700. The urine showed albumin one plus. He was febrile for a period of eight days with a temperature ranging from 100 to 101° F. The liver receded to normal size before his discharge six weeks later. The leg ulcer persisted.

On his next admission in November 1939 he complained of abdominal pain. The sclerae were yellow, and the liver was palpable and tender 4 cm below the costal margin. The spleen was not felt. The leg ulcer was still present. His temperature was 100.8° F on admission, and remained elevated for four days. The red

blood cell count was 2.3 million, white blood cells 24,500, neutrophils 88 per cent, lymphocytes 12 per cent, hemoglobin 5.5 gm. There were 3 to 4 nucleated red blood cells per 100 white blood cells. The icterus index was 50 units. He received three 500 cc transfusions. The red blood cell count rose to 2.89 million with 7 gm hemoglobin.

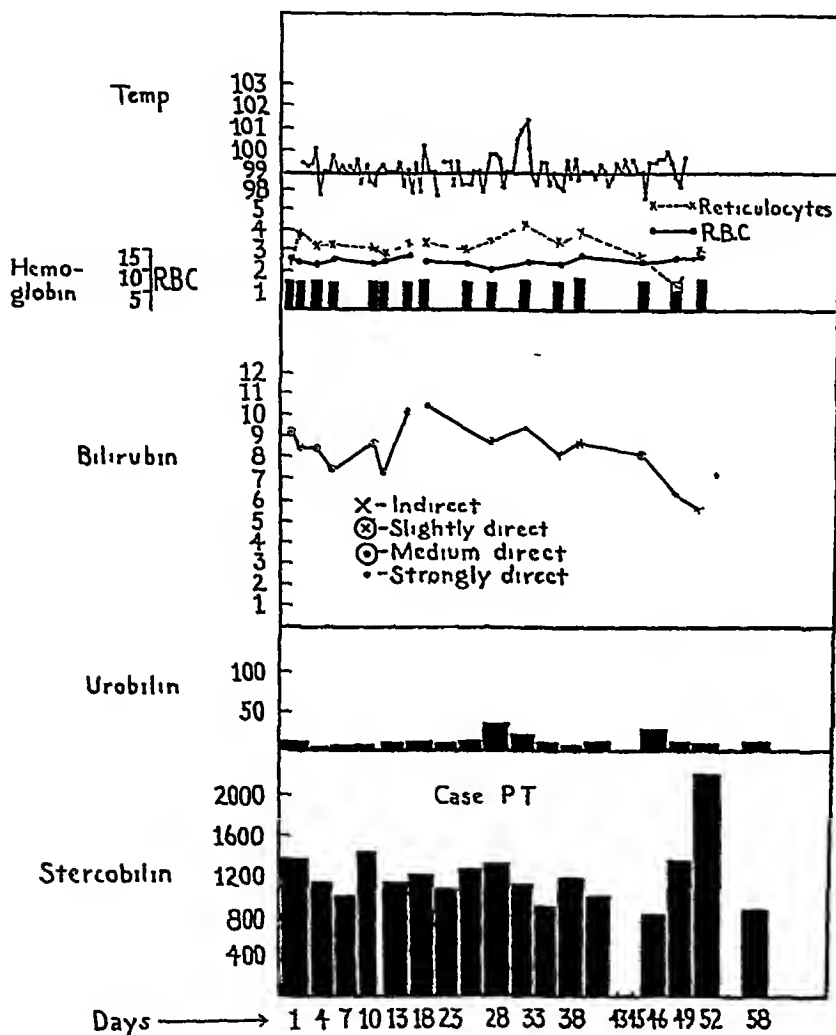


FIG 4

A month later he was admitted with the complaint of pains in his stomach. These pains were continuous, not related to eating, but were associated with anorexia and nausea, and severe headaches. There was no constipation or diarrhea. He had noticed his eyes getting yellow just a week prior to this admission.

He was a thin colored boy, temperature 104° F, blood pressure 108 mm Hg systolic and 65 mm diastolic, pulse 65. The sclerae were deeply jaundiced. The mucous membranes were quite pale. The axillary, cervical, and inguinal nodes were all enlarged. The lungs were clear. The heart was moderately enlarged to the left. The apex impulse was diffuse and forceful. There were no shocks or

thrills. There was a soft systolic murmur heard at all valve areas, but heard loudest in the third left interspace near the sternum. The liver was markedly enlarged, extending almost to the umbilicus. It was quite tender. The spleen could not be felt. There were scars and an open ulcer on each leg. Both ulcers measured 3 by 4 cm. in diameter.

The red blood cell count was 2.0 million, hemoglobin 5.0 gm., white blood cell count was 35,500, neutrophils 80 per cent, lymphocytes 16 per cent, monocytes 4 per cent, with 4 to 5 nucleated red blood cells per 100 white blood cells. The urine showed one plus albumin. The icterus index was 125 units, and it decreased in two days to 50 units.

The temperature declined to normal over a nine day period, during which time he received 900 c.c. whole blood. It then remained at normal levels with frequent rises to 99.3 to 100.3° F.

A month after his last admission our studies (figure 4) were begun, at which time his liver was still enlarged and tender. The red blood cell count was 2.3 million, hemoglobin 7 gm., white blood cells 29,100, reticulocytes 14 per cent. The bilirubinemia was 7.4 mg. per cent, with a negative direct reaction.

The data from these observations, together with the clinical picture, suggest that this patient has a more active form of the disease which has been interrupted by periods of increased activity, which though not limited to involvement of the liver, nonetheless shows the phenomena observed in case 3 and case 2. In case 2 and case 4 we probably missed the early phenomenon of excessive urobilinuria, as this is evidently rather transient. There remains the clinical liver enlargement, the elevated bilirubinemia and the direct qualitative reaction of the serum bilirubin. We feel that although there was not the excessive urobilinuria as seen in case 3, the rises to 25 to 26 mg. per day in this case during the course of the hepatomegaly is suggestive evidence of functional disturbance of the liver. The tendency to cyclic alterations in the stercobilin excretion is not so evident in this patient, but more so in the urobilinuria than heretofore noted.

### DISCUSSION •

We have been particularly interested in the apparent involvement of the liver in certain exacerbations of this disease. When we first observed it during these studies we felt that it could easily be explained by the stagnation and sickling of the red blood cells in the liver sinusoids as observed by Diggs<sup>7</sup> in the spleen and by Diggs and Ching<sup>1</sup> in the liver. Soon after case 3 of this group was studied, we observed the same phenomenon in a case of congenital hemolytic icterus<sup>11</sup> wherein the tendency to stagnation because of the stasis and the aggravated deformity of the red blood cells would not so clearly apply. This conception may, nevertheless, be pertinent in sickle cell disease, aggravating the anoxemia present in tissues, such as the liver, of those patients with the more severe anemias. Another point in favor of this idea is the marked transience of the phenomenon as is evident in case 3, the more or less frequent repetition of it and its correlation with other evidences of exacerbations of the disease process such as the activation of healed ulcerations, fever, and leukocytosis, in the absence of demonstrable infections.

This picture of acute transient hepatomegaly associated with abdominal pains, nausea, anorexia, fever, headaches, leukocytosis, and hepatogenous

jaundice, may be designated as one type of abdominal crisis which occurs in this disease as it does in congenital hemolytic anemia

It is thus far impossible to estimate the severity of the disease process on the basis of one factor alone. It is evident that the severity of a given case may vary from time to time, that in this disease as in others there are exacerbations and remissions, and that the gravity of the condition depends not only on the overall activity of the disease, but also upon what particular organ or system may be involved. Therefore, Bauer's suggestion<sup>2</sup> that the disease process be designated sickle cell disease has merit.

We have reported these four cases as representing various degrees of severity of a single syndrome as judged by the general health of the patients, tendency to exacerbations, degree of anemia, duration of the exacerbations, and the tendency of the leg ulcers to recur and to heal. It would appear that this particular type of crisis is more likely to occur and be more severe in the patients with evidences of the more marked degrees of activity.

The relationship of this transient hepatomegaly to the hepatomegaly observed by the pathologist is interesting to speculate on. Stasney<sup>6</sup> has studied the liver and spleen relationship in this disease, and described anew the marked congestion of the sinusoids and venous sinuses which seem to be the outstanding factors from a quantitative aspect. Hyperplasia and erythrophagocytosis by the Kupffer cells as well as the edema and degenerative changes of the parenchymal cells would add further to the increase in weight.

We feel that the degree of activity of the disease process is the most important factor in determining the gross and histological end results as viewed by the pathologist. On this basis Stasney's data suggest that those cases of lesser degrees of activity live longer (average age of his group I, 33.6 years) and have less pathological change (liver-spleen ratios near normal) and frequently die of secondary causes. His group II cases all showed more marked pathological changes. The average age at death of this group was 19 years. As Diggs has suggested, there is only a general correlation between spleen size and age groups, and there are notable exceptions in individual cases. It is probable that the explanation of these exceptions is to be found in the degree of activity of the pathophysiologic processes which produce the progressive histologic changes. Such processes of great intensity acting over a short period of time could cause histologic changes of the same degree as the same processes, only of lesser intensity, acting over a longer interval. Death, because of the disease or incidental complications, would interrupt the sequence at any point, thus causing apparent inconsistencies in the autopsy material.

It is this factor, the variable dynamic intensity of the disease, which is best illustrated by the clinical and laboratory material we have presented. At times it is difficult to recognize the cause and effect relationships of anatomic and physiologic changes. However, it is generally agreed that it is the genetically conditioned cellular physiologic aberration which is primary.

in sickle cell disease. How this primary physiologic fault acts to produce such evident structural defects as the abnormal red cells and the vascular and thrombotic phenomena which lead to the histologic abnormalities we do not know.

### SUMMARY

Four cases of sickle cell disease with the hemolytic syndrome of variable degrees of severity have been presented in an attempt to illustrate acute transient hepatomegaly and liver dysfunction as occurring in certain of the abdominal crises of the illness. We feel that this tendency to acute exacerbations of the disease is generally correlated with the degree of activity of the disease.

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# THE TREATMENT OF OBESITY BY APPETITE CONTROL· THE USE OF AUTONOMIC SUBSTANCES AND THEIR SYNERGISTS \*

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THE most common and important type of obesity is without doubt due to the overindulgence of food. The purpose of this paper is to discuss methods of influencing the diet in this form of obesity. There are, however, two other types although rare, that should be mentioned. Because of the prevailing confusion that these types are common they will be gone into in some detail, but it must be stressed again that they are relatively rare.

*Unusual Forms of Obesity* These rarer forms of obesity are due to glandular disturbances and lesions of the central nervous system, especially of the hypothalamus. Their relative rarity has been stressed by many recent authors, especially Greenhill<sup>1</sup>. One usually diagnoses endocrine obesity when there is excess fat around the hips and trunk and perhaps an associated amenorrhea. It is not so well known, as Greenhill points out, that fat in these parts is common in every case of obesity, and that menstrual difficulties, such as amenorrhea, hypermenorrhea or dysmenorrhea, may promptly disappear after weight loss, even without endocrine treatment.

One type of endocrine obesity is that considered to be due to pituitary deficiency. However, experimentally the removal of the pituitary actually causes loss of weight. Clinically also, in Simmonds' disease, where there is a destruction of the pituitary, emaciation is found. Froehlich's syndrome is also usually considered to be a disease of the pituitary. This condition is certainly diagnosed more commonly than it actually exists. Many young boys with undescended testicles and with fat on their hips, trunks, breast and mons veneris have been considered to have this disease without actual proof. Most of these patients become normal without any treatment whatever. The true Froehlich's syndrome is probably due to a disease of the hypothalamus rather than the pituitary. A true type of pituitary obesity is the so-called Cushing's disease or basophile adenoma of the pituitary. These patients are not remarkably obese, but their obesity is confined to the girdle region of the body and develops so rapidly that painful striae of the skin are formed. This disease is quite rare, and in addition to the moderate obesity, there are gonadal disorders, osteoporosis, hypertension and polycythemia. These serve to delineate this rare type.

The thyroid gland is seldom involved alone as a cause of obesity. In hypothyroidism fat is not greatly increased in the patient. Instead, there is a peculiar form of fluid present, as is evidenced by the term myxedema. There are, however, fat deposits on the neck and shoulder, but these are not

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extensive. It is often stated that the basal metabolic rate in obese patients is low, and therefore they have hypothyroidism. Greenhill<sup>1</sup> again points out that the basal metabolic rate as ordinarily determined is the total basal metabolism, and takes into consideration actively oxidizing tissues as well as the inactive tissues, such as fat deposits. Since in obese individuals these inert deposits predominate, they weight the basal metabolism in a negative direction. If we should calculate the basal metabolism on the ideal weight basis, most obese individuals would have high metabolic rates. This author points out the futility of giving thyroid to most of these patients, when their tissues are already burning at a high rate.

There are very few facts available to blame obesity on gonadal deficiency. True there are cases of excess fat about the buttocks and thighs that comes on after the menopause and ovariectomy, but unequivocal proof is lacking.

There are a few other exceedingly rare causes of obesity which will be grouped together. Some authorities say that all obesity may be due to increased water retention. The feeling at present seems to be that in every obese patient some water retention is present, but that this is not the sole, or for that matter, the most important cause of the obesity. Water retention is said to take place in females before the menstrual period, but this is a transient phenomenon. However, in the treatment of any case of obesity this must be taken into consideration. Another cause, which must be extremely rare, is a lack of ketogenic hormone of the anterior pituitary. It is postulated that in this condition there is a disturbance in the transportation of fat. The fat is swept into the depots and deposited there, and there is great difficulty in mobilizing it again. Another extremely uncommon cause which is said to exist in patients with tumors near the pituitary, encephalitis, chorea or certain forms of brain injury is probably due to injury to the hypothalamus. Here also there may be a deficiency in the nervous control of the fat mobilizing mechanism.

*Usual Causes of Obesity* We come now to the most common cause of obesity, i.e., exogenous obesity, or that due to overeating. It must be repeated again that the fat distribution and gonadal difficulties of an obese person might simulate an endocrine obesity, but most cases are actually due to gluttony. Even though we know the actual cause of most types of overweight, it is another matter to discern why these people overeat as they do. In many cases at least, overeating may be due to a psychic disturbance in which the individual is unprepared to meet the social demands of everyday life. Thus overeating is indulged in and obesity results. Bruch<sup>2</sup> has done a great deal of work on this subject in children. She has found that many overweight children are unhappy and maladjusted. Glandular treatment under these conditions is not only useless but harmful. The treatment is psychotherapy and diet. Greenhill<sup>1</sup> goes more deeply into the social, economic and psychic factors that cause people to overeat. An individual may have grown up in an environment where a great deal of food is eaten. He thus continues this practice of gluttony in later life, and the consequence is

overweight The overeating may be an escape mechanism for a mental conflict There is also a group of people who lack normal interests in life and obtain pleasure in overeating It is often impossible to appease their appetites because they are unable to satiate their sensory desires (Anhedonism) Another form of mental conflict considered important in females is that obesity can be an escape from competition for masculine attention In this condition overeating is an excuse It can thus be seen that in addition to any treatment outlined, psychotherapy, especially of the family-physician type, must also be used in conjunction with any form of treatment It can also be seen why such divergent reports appear in the literature on any form of treatment It is impossible to formulate statistical results on these patients because of the psychic elements involved, and because of the varying abilities of different investigators in performing psychotherapeutic treatment

*Dietary Treatment* The first and foremost principle in the treatment of obesity is the placing of the patient on a low calorie diet If this can be adhered to, no other treatment is required However, in view of the psychic elements previously mentioned, this is often impossible alone First, we have to show these patients how they will benefit by the reduction of weight In young girls one has to point out the value of an attractive figure, and in older patients one must show how obesity causes damage to the cardiovascular system As stated, the most important thing is to lower the level of food intake below the amount that is necessary to maintain the body weight It will be the object of this paper to show how this can be done in many patients During the course of treatment we must aim at the cultivation of new food habits in these patients, if our treatment is to have permanent value We must also analyze the psychological causes of overeating and explain these to the patient

In extreme obesity, Strang et al<sup>3</sup> prescribed a diet adequate in proteins, vitamins and salts, but low in fats and carbohydrates This diet consisted of about 550 calories per day, and under this régime, the subjects lost about 6/10 of a kilogram per day, over approximately a 60 day period In this extremely low carbohydrate diet, the urine must be tested for acetone frequently The partial starvation reduces weight, but since the fat stores are mobilized without adequate intake and burning of carbohydrates acidosis may supervene If the patient is less obese, a more liberal diet is prescribed which may go as high as 1,500 calories, but in our experience it is wise to limit it to from 1,000 to 1 200 calories Good foods to include in such a diet are lean meats, egg white, fresh or skimmed milk, bran muffins, 5 per cent vegetables and flavored gelatin and citrus fruits If three to five per cent vegetables are cooked in water several times, and the water thrown away, this will provide bulk with very little carbohydrate Mayonnaise made with mineral oil is a good salad dressing which is fat-free, as far as the metabolism of the organism is concerned Fat-free broth or bouillon is filling and is of negligible caloric value



Overweight individuals should be told that they must absolutely avoid the following foods

1 Mayonnaise, olives, olive oil, fatty meats, fried foods, gravy, chocolate, cocoa, ice cream and cream

2 Pastries, macaroni, sodas, alcoholic drinks, canned fruits with syrup, sweet potatoes, and white cereals such as rice and farina

The patient must eat very sparingly of the following fruits and vegetables: green peas, lima beans, potatoes, baked beans, corn, raspberries, apples, cherries, plums, bananas, prunes and grapes. These are the "15-20 per cent fruits and vegetables." The individual should also have a very limited intake of bread and butter. The patient may eat liberally of the following foods which have only a 1 to 5 per cent carbohydrate content

*Abbreviations Used in Figures*

- B Benzedrine sulphate in milligrams
- A Atropine sulphate in fraction of a grain
- T Thyroid in grains
- D Desoxyephedrine in milligrams
- G Gels, such as metamucil, one teaspoonful in orange juice
- M Mercupurin or mercuhydrin, one to two cubic centimeters intravenously
- Am Aminophyllin in 3 grain coated tablets

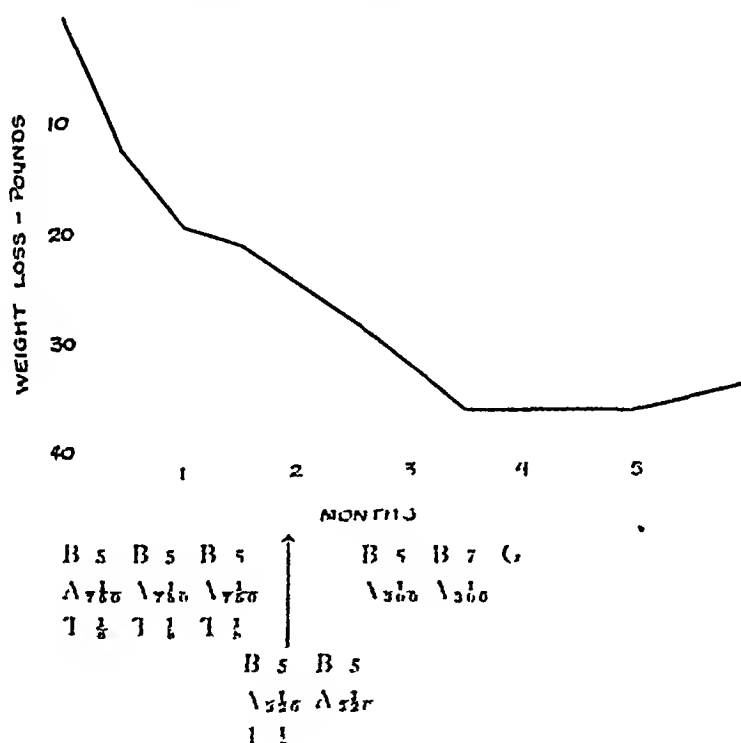


FIG. 1 C. M. F., age 32, weight 192 pounds, height 63 inches, optimum weight 140 pounds. Basal metabolic rate was minus 12. Weight gain was marked since birth of a child two years ago. Attempted to lose weight on 1,000 calorie diet and 1 gram of thyroid tid, but without success, even though this was continued for six months. Weight reduction or appetite control therapy was adequate.

They are lettuce, asparagus, spinach, beet greens, dandelion, water cress, cabbage, brussels sprouts, kale, leeks, broccoli, celery and swiss chard. A very good fruit is watermelon which has a small carbohydrate content. The patient should be cautioned against the use of too large quantities of water along with large amounts of salt. Even though water per se will not cause a weight gain, if it is taken with a sufficient quantity of salt, edema may result.

*Methods of Controlling Appetite in Obese Patients* It has been found by experience, that merely admonishing a patient to adhere to a low calorie diet has been largely unsuccessful. This has been true even though the

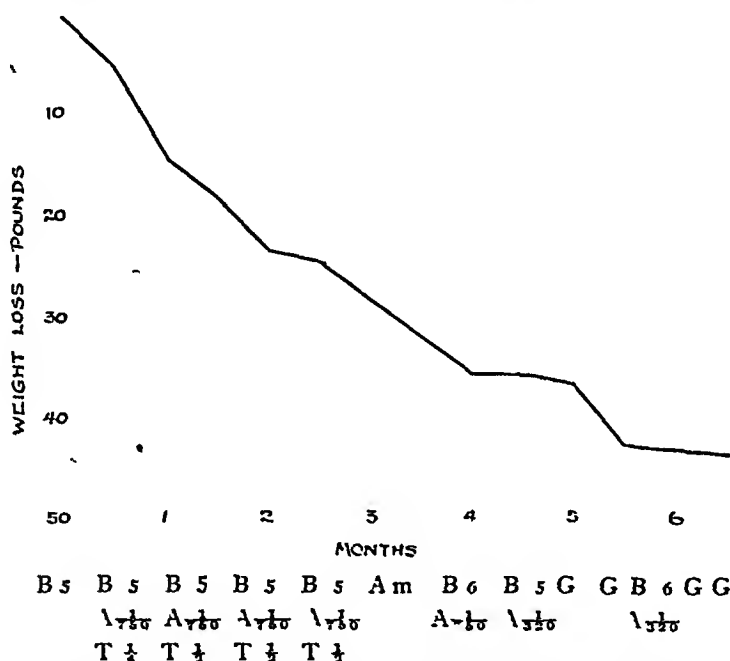


FIG 2 A McC, 1, age 48, weight 218 pounds, height 69 inches, ideal weight 163 pounds, basal metabolic rate minus 8. Weight gain was marked in past six months. In addition this patient complained of tiredness, soreness of tongue and numbness of the fingers. She had previously had an enlargement of the thyroid for which she was given a half grain thyroid tablet three times a day. Subsequently she had been on a 1,000 calorie diet and thyroid 1 grain three times a day, without loss of weight. Diet plus appetite control therapy caused an adequate loss of weight.

patient may be sincere in his attempt to lose weight. This is because adherence to a low calorie diet alone will often cause intense weakness. This may be present even though vitamin and iron medication is included. For this reason it is necessary to employ means that will curtail the appetite and at the same time would give the patients a feeling of well-being that will encourage him to continue the dietary treatment. The appetite depressants (used in this study) were benzedrine sulphate (racemic amphetamine) and atropine. The dosage of benzedrine was usually started at 5 milligrams three times a day, and increased slowly at two week intervals to about 10

milligrams three times a day Occasional cases required 12 milligrams three times a day This substance was combined with atropine, in doses starting at 1/750 of a grain and gradually increased to 1/250 grain These drugs were given together in a capsule one hour before each meal A tolerance was soon developed for each of these drugs, so that the same dose would no longer cause a reduction in appetite It was necessary, therefore, to increase the dosage of either or both of them, about every two weeks Thyroid was included if the basal metabolic rate was below minus 5 per cent The dose of thyroid which, when used, was also included in the same capsule, ranged from 1/8 of a grain to 1 grain three times a day The appetite depressing medication was found to work best when taken about one hour before meals

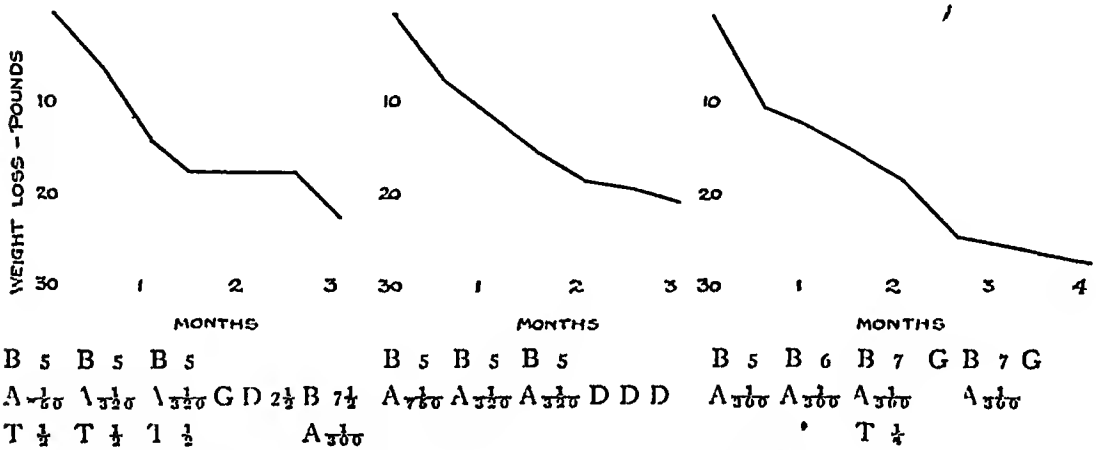


FIG 3 (left) J T, f, age 27, weight 158 pounds, height 66 inches, ideal weight 140 pounds Patient complained of irregular menstruation, swelling of feet and headaches These headaches were usually over one eye and occurred before or after her period Basal metabolic rate was minus 12 In addition, she complained of occasional breaking of her finger nails She had gained 20 pounds in the past four months, and volunteered that she could stand a great deal of heat She was tried on 1,000 calorie diet and three grains of thyroid a day This was ineffectual in causing a loss of weight, although some of her symptoms improved Coincident with the loss of weight on the new therapy, her periods became normal and swelling of feet disappeared

FIG 4 (center) M M, f, age 36, weight 151 pounds, height 63 inches, ideal weight 132 pounds, basal metabolic rate was just average normal The patient's chief complaint was migraine headache and moderate amount of overweight During her period of weight loss and dietary restriction, her headaches were few This was probably due to restriction of certain foods to which she was sensitive Weight loss was adequate on appetite control therapy

FIG 5 (right) T S, f, age 40, weight 171 pounds, height 65 inches, ideal weight 146 pounds, basal metabolic rate was just average normal Her complaints were pain in her legs, nervousness and obesity She could not take thyroid without feeling light headed Her previous attempts at weight reduction on diet therapy proved ineffectual and were abandoned easily The appetite control therapy resulted in adequate reduction of weight, which has since been maintained

Most women did not lose weight around their menstrual periods This is a well known concept and is undoubtedly due to retention of water at that time Under such conditions, aminophyllin in 3 grain tablets was given three times a day, to tide over the period of fluid retention This often caused a satisfactory reduction of weight Occasionally mercurium or mer-

culhydrin, a new mercurial, was used if aminophyllin was found to be ineffective

It was invariably found that even though weight loss had been satisfactory for several months, a point was reached when the patient became refractory to both benzedrine and atropine. This is a phenomenon that has been noted with most patients receiving these autonomic drugs. Under these conditions, it was necessary to discontinue the medication. In order for the subject not to increase his weight again, it was decided to have the

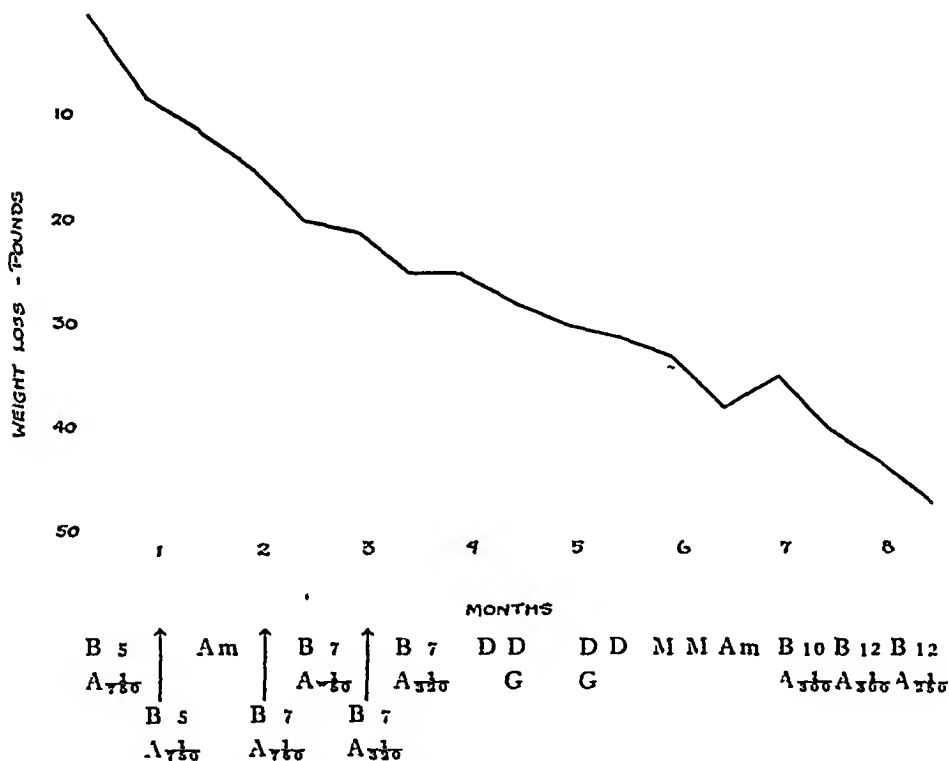


FIG 6 C. W, f, age 44, weight 270 pounds, height 64½ inches, ideal weight 145 pounds, basal metabolic rate was just average normal. This patient complained of getting tired easily and marked obesity. She has been overweight for the past 20 years, when her weight was 190 pounds. Several previous attempts at weight reduction had failed. At the start of therapy, her pulse rate was 112, blood pressure 160 mm Hg systolic and 90 mm diastolic. Under the appetite control medication her blood pressure fell to 130 mm Hg systolic and 90 mm diastolic and pulse rate decreased to 96.

patient take a gel producing substance, such as metamucil, one teaspoonful in water or orange juice, immediately before eating. Although this did not reduce the appetite sufficiently to cause a loss of weight, except occasionally, it was able to tide the patient over a period of refractoriness to the appetite control drugs. After a period of two weeks the autonomic drugs could be resumed again in smaller amounts, with adequate control of appetite.

Several patients were also tried on desoxyephedrine in doses of 2½ milligrams three times a day. This produced in some cases a satisfactory

ILLUSTRATIVE DIET LIST <sup>4</sup>

Your total calories should not exceed \_ \_ \_ for each day Divide them as directed below  
*Do not eat between meals* Some exercise must go with this diet daily

## BREAKFAST

You may select from below calories

	Calories		Calories
1/2 medium orange	25	1/2 cup cornflakes	50
1/4 small grapefruit	20	The average glass of milk	125
3 cooked prunes	45	1 glass of skimmed milk	70
1 teaspoon butter	50	1/2 tablespoonful heavy cream	35
1/2 cup oatmeal	75	1 teaspoon sugar	25
1/2 cup of cream of wheat	75	1 Uneda biscuit	20
1 slice rye or white bread	50	Tea or coffee with no sugar	0

## LUNCH

You may select from below calories

	Calories		Calories
8 small asparagus tips	20	3/4 cup cooked cabbage	25
2/3 cup brussel sprouts	20	1/2 cup eggplant	25
3 stalks fresh celery	15	2 small green peppers	25
10 slices cucumber	15	1/2 cup stringbeans	25
1/4 small head lettuce	15	1 medium fresh tomato	20
1/2 cup cooked spinach	30	3/4 cup carrots	40
1/2 cup canned tuna fish	50	3/4 cup turnips	35
1/2 cup canned salmon	100	1 small apple	55
1/4 cup cottage cheese	65	1/2 cup muskmelon	40
1 slice rye or white bread	50	Tea or coffee with no sugar	0

## DINNER

You may select from below calories

	Calories		Calories
1 cup vegetable soup	75	2 slices roast veal	80
1 cup spinach soup	85	1 slice breast chicken	60
1 cup beet soup	90	1/2 small chicken broiler	75
2 slices lean roast beef	85	1 egg	75
2 cakes hamburger steaks	85	1 piece 2 x 3" Haddock	35
1 portion lean round steak	85	6 large oysters	40
2 slices lean roast lamb	95	1 piece brook trout	45
1 slice rye or white bread	50	Tea or coffee with no sugar	0

Bread, beverages, fruit, etc from the above list, may be added to any meal provided the total calories do not exceed the amount prescribed

## THE FOLLOWING FOODS MUST BE AVOIDED

Nuts, olives, olive oil, chocolate and cocoa, gravy, cream soups, sauces, ice cream, candy, pastry, macaroni, potatoes, alcoholic beverages, canned fruits in syrup, and highly spiced and salted foods Do not use sugar unless you absolutely have to  
 Four glasses of water each day are allowed Be sure that your daily menus include a fresh fruit, either meat, fish or egg, milk and three vegetables

appetite reduction which, however, continued only a short period of time. In most cases, side actions were too marked to advise further use of this drug, and it was therefore discontinued

*Case Records* This report covers 150 privately treated cases of obesity It was found that these private patients were better subjects, because most of them genuinely wanted to lose weight There was also more time to study the possible psychic causes for the obesity, and an attempt made to treat them with a certain amount of psychotherapy The study has been continuing for the past one and a half years It has been almost uniformly

successful, although seven absolute failures were encountered. Some of these occurred at the outset of the project when very small doses of the substances were used. As experience was gained with the use of these drugs, it was found that only rarely was a rise in blood pressure or pulse rate seen. Thus, it is obvious why opinion on the value of these drugs varies so much, and why statistical analysis does not give an accurate picture. Each patient requires an individual dose of each drug, and also requires an increase at a different rate. Some psychotherapy is also required in the case of each patient, either during the treatment, or certainly after the treatment is discontinued. New eating habits must be established if a patient is not to regain his lost weight. All the female patients require some form of diuretic therapy during, and often following, the menstrual period. All the patients develop a refractoriness to the therapy, and therefore require a short period of rest. We have used the gel treatment in this interval. This same substance is usually required for some period after satisfactory weight loss has been reached, and until new eating habits have been thoroughly established. If this does not occur, the whole treatment has been wasted (figures 1-6).

*Possible Mode of Action of the Drugs Used in This Study* A Benzedrine. Many authors have reported that benzedrine sulphate reduces appetite. At first it was accidentally discovered during its use for central nervous system stimulation<sup>5, 6</sup>. Subsequently it was used for this definite purpose. The theories of its action are many, and vary with the different authors. We feel, however, that its action is definite. These actions are said to be as follows:

1 Stimulation of motor activity<sup>5, 6, 7</sup>. This action certainly could not be the most important one, because under such conditions food intake would be proportionately increased, which would defeat the purpose of the drug.

2 Slowing of digestion<sup>8, 9, 10</sup>. It has been shown that benzedrine sulphate delays emptying time of the stomach<sup>11, 12</sup> and often decreases intestinal peristalsis<sup>13</sup>. However, the depression of appetite is often present with doses too tiny to cause delay in stomach emptying time and a decrease in peristalsis of the intestinal tract<sup>8, 9</sup>.

3 Improvement of mood. It has been noted that apathetic obese patients often overeat because of the impairment of satisfaction of their sensory desires<sup>7, 9, 10</sup>. This has been explained elsewhere in this paper. Often these patients respond dramatically to benzedrine and the other synergistic drugs used. The increased mental activity might conceivably distract the patient from an inordinate desire to satisfy his reactions by the intake of food.

4 Metabolic effect. Some authors<sup>14</sup> attribute weight loss in benzedrine treated cases to an increase in the basal metabolic rate. This has been largely repudiated. In our own series, when benzedrine and atropine were taken without thyroid, there was no rise in the basal metabolic rate.

5 Water retention One author<sup>9</sup> suggested that the initial weight loss (with benzedrine) might be due to inhibition of water retention, since benzedrine seems to induce a loss of weight even when the caloric intake was increased. There is some justification for this theory in several cases in our series. When combining a mercurial diuretic by injection with benzedrine by mouth a more impressive weight loss occurred than by using the mercurial alone or in combination with the gel.

6 Hypothalamic stimulation Bruch<sup>15</sup> stated that since benzedrine is supposed to be a hypothalamic stimulant, it might be reasonable to suppose that it affects fat metabolism as well as appetite by way of the hypothalamus. It has been assumed to act directly on the appetite center.

Occasional reactions may occur, including headache, restlessness, insomnia, irritability, palpitation and a disturbance of the bowel habit. However, it is necessary to state that these reactions are exceedingly few, and are merely mentioned to call attention to their rarity. It has been necessary only in a few cases to add phenobarbital at night because of insomnia. It was not found that the treatment resulted in an increase in blood pressure. Contrariwise it was often noted, as Rosenberg<sup>8</sup> has stated, that the high blood pressure usually fell in proportion to the weight loss. It was found that the atropine sulphate in the capsule would counteract some of these reactions, because they were exceedingly infrequent when the combined therapy was used. Because of the relaxing effect of the drugs on intestinal musculature, constipation usually resulted and a mild laxative was advised.

The patient must be put on vitamin-mineral supplements as soon as therapy is started, because his dietary intake will often be erratic. In practice, the patient is put on at least one potent pan-vitamin capsule, along with two ferrous sulphate tablets in 3 to 5 grain dosage. It was found that these preparations are best given at night, so as not to confuse the patient.

B Atropine Atropine as an appetite depressant has recently been popularized by Greene<sup>17</sup>. This author employed belladonna alone, and in combination with phenobarbital in a series of 25 patients to control the appetite. This drug was first used for this purpose by Franke<sup>18</sup> in 1913. He found that atropine in the form of belladonna, 15 drops of the tincture, given three times a day, 15 to 20 minutes before meals, resulted in appetite depression. At the end of his article this author posed the question whether belladonna merely has a sedative effect on the stomach, or whether it also inhibits the gastric secretion and perhaps also affects the musculature of the stomach. The answers to these questions are still not entirely known.

C Gels<sup>11</sup> It was found necessary to use something that would mechanically decrease the amount of food ingested when the patient became refractory to the appetite depressing drugs. For this purpose one of the gels, metamucil, was used, one teaspoonful being dissolved in a glass of water or orange juice three times a day, taken immediately before meals. Although in some few cases, this resulted in an actual diminution in the intake of food and a further loss of weight the usual result was merely a

lack of weight gain. This was a very useful phenomenon. During this period, usually about two weeks, when these gels were used an apparent letdown of mood occurred, in which the patient did not feel as strong as he had previously felt. This period was also a good time in which to stress the value of new food habits.

**D Diuretics** For reasons already sufficiently discussed, most patients require a diuretic during their course of treatment. For this purpose aminophyllin in 3 grain coated tablets was used. If, in a week, this was unsuccessful in causing a further loss of weight, either mercupurin or mercurhydrin was given. These preparations were usually given in 1 or 2 c c doses intravenously. In some cases, the diuretic effect was increased by continuing the benzedrine during the period of diuresis. Of course, urine examination was done before and after the mercurial therapy. In no case was there a change noted in the urine. It was also necessary to give mercurials in male patients. There must be water retention in probably every case of obesity, either male or female, although it is not of a cyclic type in the former.

**Diet** The patient should always be given a diet of about 1,000 calories. This will probably not be exceeded during the period of the use of the autonomic drugs. However, the patient should have a diet list to refer to during the period of refractoriness to the drugs and for guidance in the formation of a sound habit. A diet list<sup>4</sup> such as is given to my patients is included here. The calories may be divided as follows: 150 for breakfast, 250 for lunch and 600 for dinner. This may be varied according to the patients.

**Exercise** Exercise is of benefit in the management of the obese patient for two reasons. One is for the general stimulation of motor activity which occurs during exercise, and the other because exercise helps the patient reduce in certain areas that the patient desires. These exercises may also include massage, and other passive types of exercise, but it should be realized, as Newburgh<sup>20</sup> points out, that the muscular activity indulged in by the attendant is incapable of increasing the heat production of the patient. The patient must do the work, if he is to dissipate the energy. Exercise alone is usually not sufficient to cause an adequate loss of weight, and is a much harder way of reducing than by limitation of food intake through appetite depression.

### SUMMARY

The causes of obesity are discussed at some length. It was found that the most important cause of overweight is overindulgence of food. Several ways of reducing the appetite have been found effective in the treatment of 150 patients over a period of one and a half years. In order to achieve permanent results, the patient must be shown the reason for his obesity and the advantages that weight loss would give him. There must



also be an attempt to create new food habits so that the loss of weight may be permanent

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# EVALUATION OF THE ERYTHROCYTE SEDIMENTATION TEST IN LEPROSY: STATISTICAL STUDY OF MORE THAN TWO THOUSAND TESTS IN MORE THAN FIVE HUNDRED PATIENTS \*

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THE changes in the erythrocyte sedimentation test which occur during the course of leprosy have not been studied as thoroughly as they have in tuberculosis. Although this laboratory procedure has been employed in both diseases for approximately the same period of time, it has met with great popularity in tuberculosis whereas comparatively few articles on the subject are extant in the literature on leprosy. Not all investigators are in accord as to the significance of this test in leprosy. Many, including Landeiro,<sup>1</sup> Muir,<sup>2</sup> and Schujman,<sup>3</sup> report that it bears a close relationship to the type of disease, being rapid in the lepromatous (nodular) and mixed types and often approaching normal in the neural form. Some writers, Muir<sup>4</sup> and Kerr,<sup>5</sup> find special use for the sedimentation index as a test of the patient's tolerance to medication, particularly his reaction to the iodides.

## PRESENT STUDY

The present report is based upon 2023 erythrocyte sedimentation tests made on 510 patients with different types of leprosy at the National Leprosarium. The period of observation varied from eight months to four years. The 510 patients were divided according to sex into 338 males and 172 females. Their ages varied from six to 82 years, the great majority being between 20 and 40 years.

The patients were classified as to types of disease into 384 lepromatous or mixed cases, 108 neural cases and 18 tuberculoid cases. The lepromatous and mixed cases were classified together for greater convenience, as it was difficult at times to separate them clinically. There were many borderline cases that might have been included in either group, depending upon the thoroughness of the neurologic examination. Also, during the prolonged period of study the disease frequently changed from the lepromatous to the mixed type. Since it is the lepromatous lesions which carry the grave prognosis and the superimposition of neural lesions is of little added consequence, it would have served no useful purpose to separate the mixed from the lepromatous cases.

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## TECHNIC

The technic used in this study was the Cutler sedimentation test modified only by the substitution of oxalates for sodium citrate as the anticoagulant. The proportion of potassium and ammonium oxalates used (4 mg of potassium oxalate and 6 mg of ammonium oxalate for 5 c.c. of blood) is that recommended by Heller and Paul<sup>6</sup> as giving minimal shrinkage of the erythrocytes. This anticoagulant is advocated also by Kolmer and Boerner<sup>7</sup> and Wintrobe and Landsberg.<sup>8</sup> It proved entirely satisfactory at the National Leprosarium. An additional advantage was that the same sample of blood could be used for blood chemistry. In a series of duplicate sedimentation tests on a group of patients, using 3.8 per cent sodium citrate for one test and the potassium and ammonium oxalates for the other, the writer obtained closely comparable results.

## RELATIONSHIP OF SEDIMENTATION TEST TO TYPE AND EXTENT OF LEPROSY

The erythrocyte sedimentation test is at best a crude laboratory procedure. Nevertheless, within certain limitations, it has a practical value as an estimation of the amount of tissue destruction which is taking place in the body. Muir<sup>4</sup> asserts that "uncomplicated leprosy, however heavy the infection, does not of itself accelerate sedimentation." This was not the experience at Carville. In this leprosarium, on the contrary, uncomplicated leprosy, even when the general health of the patient was otherwise good, produced a rapid sedimentation. This occurred in all types of leprosy, although to a greater

TABLE I

Distribution of Total Erythrocyte Sedimentation Tests Among the Different Types of Leprosy

Type of Disease	Sedimentation rate in mm. at the end of an hour (Cutler)								Total
	0-5	6-10	11-15	16-20	21-25	26-30	31-35	36-40 +	
Tuberculoid	14	8	7	6	7	4	0	0	46
Neural	54	88	107	121	90	14	5	0	479
Lepromatous and mixed	20	35	82	208	575	441	116	21	1,498
Total	88	131	196	335	672	459	121	21	2,023

extent in the lepromatous and mixed cases. Even patients with arrested leprosy of a number of years' duration seldom had normal sedimentation records. Leprosy is classified as arrested at the National Leprosarium only after a patient has had bacteriologically negative skin and nasal smears for 12 consecutive months and is declared free from clinical evidence of activity by a medical parole board.

Occasionally, sedimentation indices approaching normal were encountered in patients with minimal or discrete lesions, whether of the lepromatous or neural type. Thus, although tuberculoid and neural cases as a group had

slower blood sedimentation rates, in individual cases the extent as well as the type of the disease exerted an influence on the test. Very exceptionally, patients with far advanced disease for some unknown reason showed normal sedimentation tests. These paradoxical findings occurred in three patients at the National Leprosarium. In each instance, a repetition of the test after several months had elapsed resulted in a reversion to an abnormal zone more consistent with the patient's condition.

Table 1 shows the total number of sedimentation tests made at the National Leprosarium, distributed according to the type of the disease and without regard to the individual patient.

Table 2 shows the average sedimentation index of all tests made on each of the 510 patients. The patients are classified according to the type of the disease. Both tables demonstrate, but table 2 more clearly, that the sedimentation rates increase in order from the tuberculoid to the neural and finally to the lepromatous and mixed types of leprosy. In a supplement to table 2 the definite effect of trophic ulcers in increasing the sedimentation indices of neural cases is shown.

TABLE II

Average Sedimentation Index of Leprosy Patients Classified According to Types of Disease

Types of Disease	Sedimentation rate in mm at the end of an hour (Cutler)								Total
	0-5	6-10	11-15	16-20	21-25	26-30	31-35	36+	
Tuberculoid	5	4	2	5	1	1	0	0	18
Neural	5	19	28	31	21	3	1	0	108
Lepromatous and mixed	0	7	12	48	151	131	28	7	384
Total	10	30	42	84	173	135	29	7	510

TABLE II-X

Average Sedimentation Index in Neural Cases with and without Trophic Ulcers

	Sedimentation rate in mm at the end of an hour (Cutler)								
	0-5	6-10	11-15	16-20	21-25	26-30	31-35	36+	
Neural cases with large trophic ulcers	0	0	1	3	12	3	1	0	20
Non-ulcerated neural cases	5	19	27	28	9	0	0	0	88

Table 3 shows the average sedimentation rates of the 510 patients classified as to extent of the disease in its different types. It demonstrates that the stage of advance of leprosy exerts a definite influence upon the acceleration of sedimentation of the red blood cells in every type of the disease.

Table 4 gives the sedimentation tests in bacteriologically negative as compared with bacteriologically positive cases of leprosy. In 79 per cent of negative cases the sedimentation rate was less than 20 mm, whereas in 78 per cent of positive cases it was more than 20 mm.

TABLE III  
Average Sedimentation Index in Relation to Stage of the Disease

Type	Stage of Disease	Sedimentation rate in mm at end of an hour (Cutler)									Type Grand Total
		0-5	6-10	11-15	16-20	21-25	26-30	31-35	36+	Total	
Tuberculoid	Minor	5	4	1	1	0	0	0	0	11	
	Major	0	0	1	4	1	1	0	0	7	18
Neural	Minimal	4	10	8	3	0	0	0	0	25	
	Moderately advanced	1	9	17	20	7	0	0	0	54	
	Far advanced	0	0	3	8	14	3	1	0	29	108
Lepromatous and mixed	Minimal	0	7	6	6	8	0	0	0	27	
	Moderately advanced	0	0	6	41	125	35	2	0	209	
	Far advanced	0	0	0	1	18	96	26	7	148	384
Grand Total		10	30	42	84	173	135	29	7	510	510

TABLE IV  
Average of Sedimentation Tests in Bacteriologically Positive and Negative Cases of Leprosy

Bacterioscopy	Sedimentation rate in mm at the end of an hour (Cutler)								
	0-5	6-10	11-15	16-20	21-25	26-30	31-35	36+	Total
Negative	6	16	19	30	14	3	1	0	89
Positive	4	14	23	54	159	132	28	7	421
Total	10	30	42	84	173	135	29	7	510

TABLE V  
Average of Sedimentation Tests in Arrested Cases of Leprosy

	Sedimentation rate in mm at the end of an hour (Cutler)								
	0-5	6-10	11-15	16-20	21-25	26-30	31-35	36+	Total
Arrested cases	3	10	17	20	13	0	0	0	63

Table 5 shows the average sedimentation rates of 63 patients who have arrested cases of leprosy. In many of these patients the disease has remained arrested for more than one year and in a few for more than 10 years. It can be noted that 13, or only 20 per cent, are within or near the normal range. An equal number, on the contrary, are within the 21 to 25 mm zone, generally considered as indicating disease activity. A considerable number of

the latter group have permanent deformities and mutilations resulting from the nerve destruction of leprosy. The results of the sedimentation test in arrested leprosy suggest that disintegration in the nerves or other tissues is probably still slowly progressing in latent leprosy.

Because, as a rule, the erythrocyte sedimentation rates do not revert to normal in arrested cases of leprosy, the value of this test is considerably limited in a leprosarium. The changes occurring in leprosy are very slow in development. The healing process, when it occurs, is of prolonged evolution. Consequently, changes in the sedimentation rates in patients with leprosy take place only after long intervals of time. For this reason, this test is of relatively less significance in leprosy than it is in tuberculosis where the healing and breaking down processes in the tissues are proportionally more rapid. It is also the writer's impression, from experience with both diseases,<sup>9</sup> that there is a relatively greater deviation from normal in leprosy than in tuberculosis when comparing minimal, moderately advanced and far advanced stages of both diseases.

Experience at the National Leprosarium showed that six months was usually a sufficiently short period between tests to record any information contributed by the sedimentation reaction in leprosy. This test was found to be generally not sensitive enough to predict improvement or aggravation in leprosy. Thus, it was usually too tardy to detect a patient's tolerance to new therapeutic procedures.

TABLE VI  
Last Sedimentation Test Preceding Death by Less Than 6 Months

	Sedimentation rate in mm at the end of an hour (Cutler)								Total
	0-5	6-10	11-15	16-20	21-25	26-30	31-35	36+	
Deaths	0	0	0	3	8	28	22	14	75

Table 6 gives the last sedimentation test performed before death on 75 patients who died at the National Leprosarium. Most of the tests preceded death by three to six months. It will be noted that the sedimentation index of 88 per cent was more than 26 mm and that of 48 per cent more than 31 mm. Since few patients except those approaching death ever attain such extremely high rates, the bracket above 30 mm may be considered as the danger zone presaging death in leprosy.

#### SEDIMENTATION ZONES

Experience at the National Leprosarium has led to the classification of the sedimentation rates into various zones of different prognostic significance. It was found that patients whose blood sedimentation consistently fell within one of these zones showed a relatively more or less favorable reaction to the disease in comparison with those whose blood sedimentation was recorded in

higher or lower zones. Also, changes from one zone to another were an indication that the patient was improving or getting worse according to whether the sedimentation rates were rising or falling. After considerable experience, the following zones have been designated:

- Zone 1, from 0 to 10 mm —normal zone, or zone of arrest of leprosy
- Zone 2, from 11 to 20 mm —zone of quiescence or slight activity of leprosy
- Zone 3, from 21 to 25 mm —zone of moderate activity of leprosy
- Zone 4, from 26 to 30 mm —zone of severe activity of leprosy.
- Zone 5, from 31 to 40 mm —danger zone, or death zone of advanced leprosy

It was observed that in cases of leprosy in which repeated sedimentation tests were below 10 mm or rarely rose into the second zone the prognosis was favorable and there was a tendency for the disease to become arrested. Such patients had minimal lepromatous lesions or had mild cases of neural or tuberculoid leprosy. A sedimentation index falling within the second zone signified that the patient was reacting fairly well to the disease and its treatment. These patients had slight cases of lepromatous or mixed leprosy or

TABLE VII  
Classification of Patients into Prognostic Zones According to the Average of Their Series of Sedimentation Tests

Zones		Number of Patients	Percentage
Zone I, Normal (0-10 mm )	Arrested or quiescent disease, good prognosis	40	7.8
Zone II, Low (11-20 mm )	Slightly active or quiescent disease Fair prognosis	126	24.7
Zone III, High (21-25 mm )	Active disease, guarded or poor prognosis	173	33.9
Zone IV, High (26-30 mm )	Very active and progressive disease or advanced disease Poor prognosis	135	26.5
Zone V, Ultra high (31 mm +).	Far advanced active disease, terminal stage Hopeless prognosis Death near	36	7.1
Total		510	100

active neural or tuberculoid types of the disease. In the largest number of patients the sedimentation index was recorded in the third zone. These patients usually had moderately advanced disease of the lepromatous or mixed type with guarded prognosis. Occasional neural cases with large infected trophic ulcers or extensive mutilations were also in this group. Patients with sedimentations in the fourth zone had, as a rule, far advanced lepromatous leprosy with poor prognosis. Patients whose sedimentation ranged above 30 mm were generally in the terminal stages of the disease and approaching death. Such patients seldom survived more than two years.

Table 7 shows the classification of the 510 patients into the different sedimentation zones according to the average of all the sedimentation tests made on them during the period of study.

## SEDIMENTATION PATTERNS

By now it must be evident to the reader that a single sedimentation test is of little practical value in leprosy. A series of tests made on the same patient during a long period, usually several years, is of some significance and may indicate the general trend of the course of the disease. From experience at the National Leprosarium it was learned that serial sedimentation tests on individual patients conformed to certain patterns. These different patterns were of four types, each suggesting a different mode of reaction to the disease. These four patterns have been designated as follows:

- 1 Horizontal sedimentation curve, prognosis dependent upon height of curve
- 2 Irregular sedimentation curve, guarded prognosis
- 3 Ascending sedimentation curve, poor prognosis
- 4 Descending sedimentation curve, good prognosis

TABLE VIII  
Serial Sedimentation Patterns in Leprosy

Type of Serial Sedimentation Curve	Number of Patients	Percentage
Horizontal	137	49
Irregular	67	24
Ascending	47	17
Descending	28	10
Total	279	100

Table 8 shows the classification of 279 patients in whom four or more erythrocyte sedimentation tests were made during the course of two to four years into the above four patterns. It was found that in 137 of these patients, or 49 per cent, the sedimentation curve conformed to the horizontal type, in 67, or 24 per cent, it was of the irregular type, in 47, or 17 per cent, of the ascending type, and in 28, or 10 per cent, of the descending type.

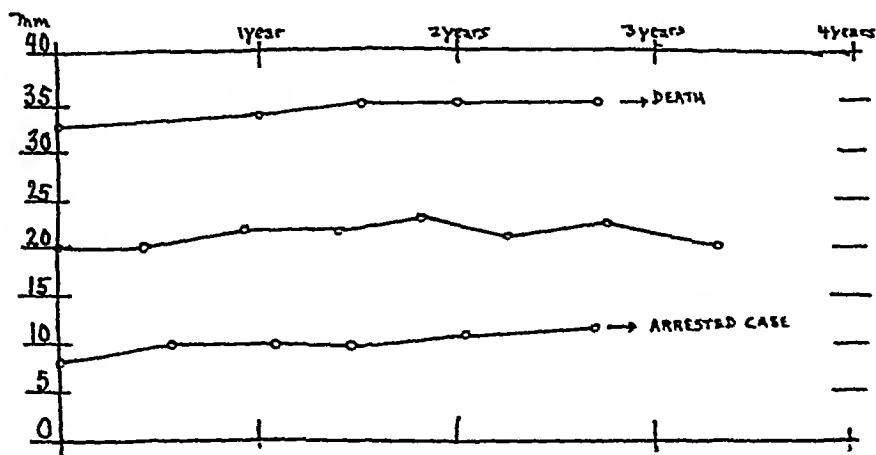


FIG 1 Horizontal curves



A horizontal or level curve usually occurred when the disease was stationary or showing little change during the course of years. A horizontal sedimentation curve of very high level, since it remained within an extremely abnormal zone, generally accompanied an advanced disease of unfavorable prognosis. When the horizontal pattern was in a low zone, approaching

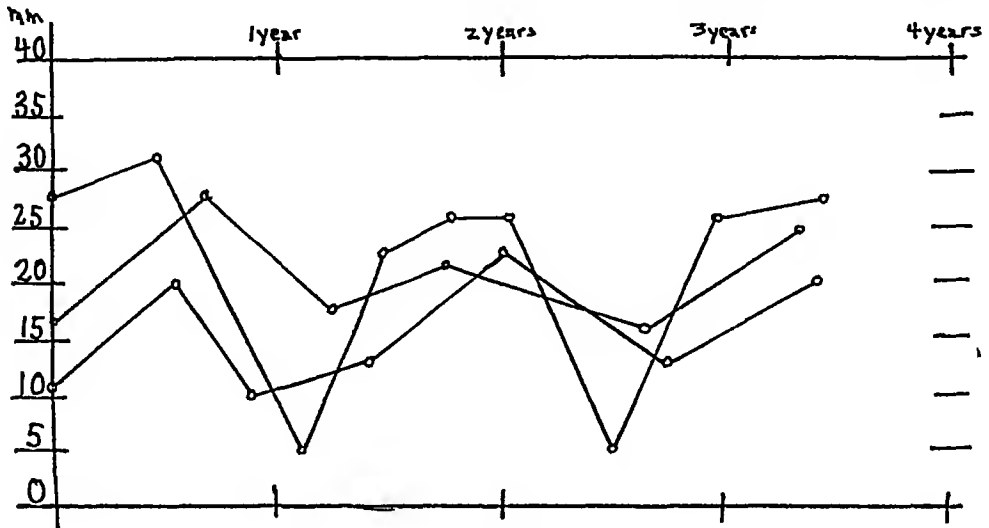


FIG 2 Irregular curves

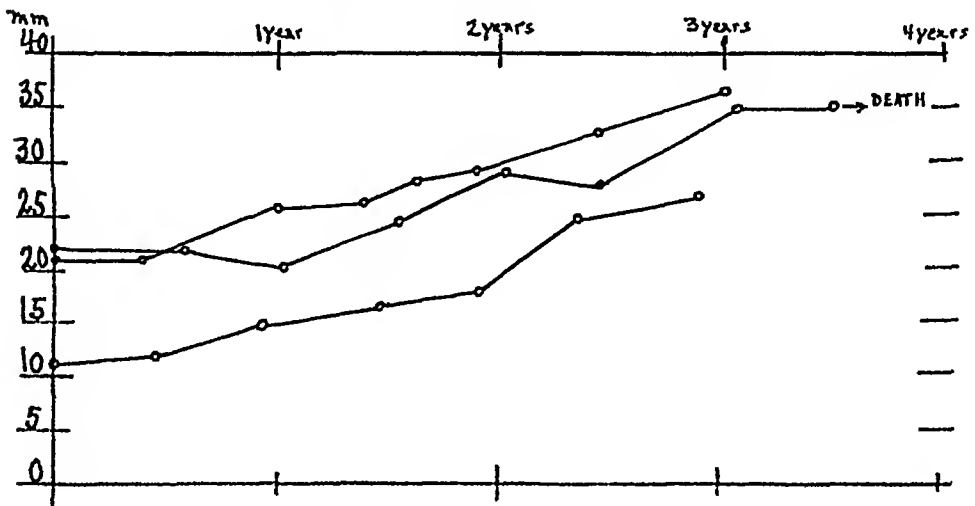


FIG 3 Ascending curves

normal, it was usually associated with minimal disease or with a neutral type of good prognosis. Horizontal curves of intermediate zones were of corresponding prognostic significance. Figure 1 illustrates horizontal curves of different levels in three individual cases of leprosy of different severity. The patient with the consistently high sedimentation is now dead, whereas the one in the low zone is at present an arrested case.

Patients with irregular or bizarre sedimentation curves had guarded prognosis. Peaks in such curves are commonly due to severe complications,

intercurrent diseases, or acute leprae reactions. The valleys resulted from temporary remissions in the disease, healing of ulcerations or unknown causes. Figure 2 illustrates the bizarre sedimentation curves of three patients.

An ascending sedimentation curve, as a rule, indicated a disease which was progressing unfavorably. Figure 3 illustrates three such curves among the patients at the National Leprosarium. In one case death was the outcome.

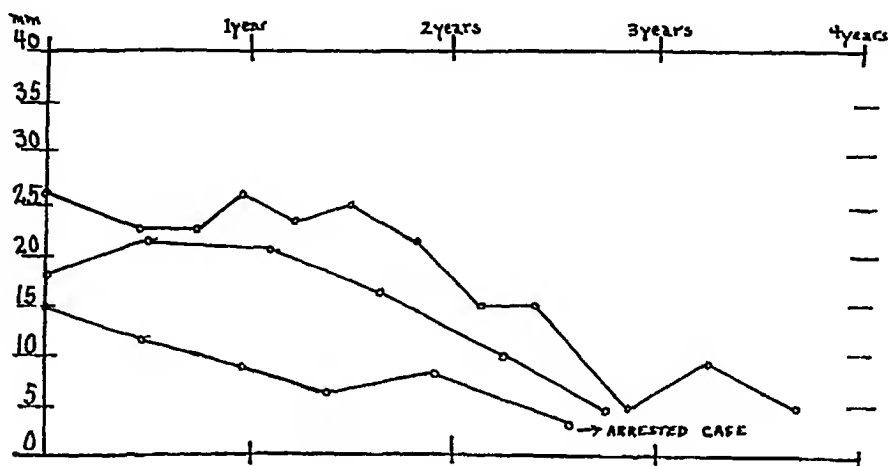


FIG 4 Descending curves

A descending sedimentation curve usually accompanied improvement and suggested a favorable prognosis. Figure 4 demonstrates such curves in three patients. In one case leprosy became arrested.

#### EFFECTS OF COMPLICATIONS AND INTERCURRENT DISEASES UPON THE SEDIMENTATION TEST

Intercurrent diseases and the severe complications of leprosy were found frequently to have an accelerating effect upon the sedimentation rate. Experience at the National Leprosarium was that intercurrent diseases, such as tuberculosis, malaria, syphilis, malignancy and others, had relatively less potent effect upon the sedimentation reaction in leprosy than had the serious complications of the disease. Tuberculosis complicating leprosy did not seem seriously to alter the settling velocity of the red blood cells. Malignancy likewise did not seem unduly to accelerate the reaction, the few patients dying of malignancy had lower rates of blood sedimentation than those dying of leprosy without malignancy.

Nephritis and secondary anemia caused considerable increase in the red cell sedimentation rate in leprosy. It was felt that leprosy as a systemic disease in its dissemination throughout the body was directly or indirectly responsible for these two pathologic conditions. They developed in the

majority of cases, in the advanced or terminal stage of leprosy. Leprous ulcerations, both mucosal and cutaneous, and trophic ulcers have a great accelerating influence on the rate of settling of the erythrocytes. This was particularly true when there was secondary pyogenic infection, which was the rule rather than the exception in leprosy ulcerations. Acute lepra reactions also caused a temporary rise in the sedimentation index, which generally lagged in returning to its prior level after the febrile reaction and skin eruption subsided.

TABLE IX  
Effects of Complications and Intercurrent Diseases upon the Sedimentation Index in Leprosy

Complicated and Intercurrent diseases	Sedimentation rates in mm at the end of an hour (Cutler)							
	0-5	6-10	11-15	16-20	21-25	26-30	31-35	36-40+
Leprous and trophic ulcers	0	0	0	2	12	36	15	1
Leprous laryngitis	0	0	0	0	1	15	6	0
Nephritis	0	0	0	0	1	9	17	11
Acute lepra reactions	0	0	0	2	23	27	7	0
Tuberculosis	0	0	1	3	5	9	2	0
Malignancy	0	0	0	2	2	4	1	0

Table 9 records the sedimentation indices of patients with severe complications or intercurrent diseases. It can be seen that such complications of leprosy as leprosy and trophic ulcers, leprosy laryngitis, nephritis and acute lepra reactions had a greater effect in lessening the suspension stability of the erythrocytes than had such intercurrent diseases as tuberculosis and malignancy.

Figure 5 depicts the effect of acute lepra reactions and the subsequent

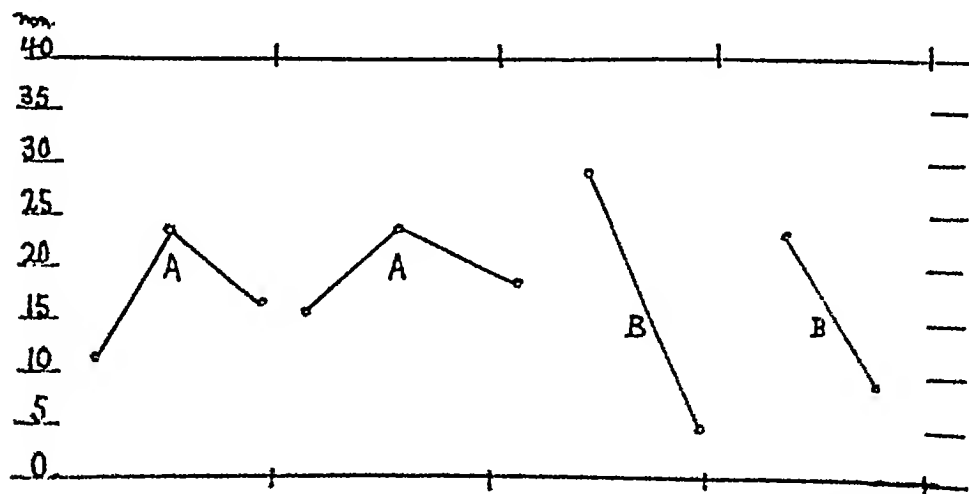


FIG. 5. Change in sedimentation rate due to (A) acute lepra reactions, (B) healing of the lesions.

recovery therefrom upon the sedimentation test. It also shows the beneficial effect of healing large infected leprous and trophic ulcers.

#### CORRELATION BETWEEN HYPERGLOBULINEMIA AND RAPID SEDIMENTATION IN LEPROSY

The erythrocyte sedimentation test may be considered as a gauge of the amount of the products of tissue destruction which are absorbed into the blood stream. These tissue products are not exactly known but are probably represented in the protein portion of blood plasma. It has been repeatedly demonstrated that the causative agent of the sedimentation of the red blood cells is contained in the liquid portion of the blood and not in the erythrocytes. It is also known that the tissue changes in leprosy result in the absorption by the blood of abnormally large amounts of globulins. The writer believes that the same tissue changes which are responsible for the excessive accumulation of globulins in the blood in leprosy also account for the presence of the abnormal tissue products which result in increased erythrocyte sedimentation rates. It can be reasoned, therefore, that, depending upon the activity and the extent of the disease, there will be absorbed into the blood stream proportionate amounts of globulins and of tissue substances responsible for the rapidity of the erythrocyte sedimentation. It was thus considered interesting to study the content of serum globulin in relation to the speed of blood sedimentation in leprosy in the same samples of blood.

TABLE X  
Correlation Between Serum Globulin and Sedimentation Test in Leprosy

Globulin content of blood	Sedimentation rate in mm at the end of an hour (Cutler)				
	1-10 mm /hr	11-20 mm /hr	21-30 mm /hr	31-40 mm /hr	Total
Low, less than 1.7 per cent	2	2	2	1	7
Normal, 1.7 to 3.25 per cent	10	12	16	5	43
High, 3.3 to 6.2 per cent	1	19	42	15	77
Per cent of hyperglobulinemia	8%	58%	70%	71%	
Total	13	33	60	21	127

Table 10 shows the results of this comparison. The two laboratory procedures were carried out on the same blood samples in 127 patients with different types of leprosy. The normal range of serum globulin, from 1.7 to 3.22 per cent, is that given by Rowe<sup>10</sup> after a review of the literature. For convenience the cases were divided into three groups: those with low serum globulin, those with normal serum globulin and those with hyperglobulinemia. It is observed that the range of sedimentation coincides closely with the globulin content of the patient's blood.

## CONCLUSIONS

The erythrocyte sedimentation test is found to be accelerated in all types of leprosy

Although the greatest deviation from normal is encountered in the lepromatous and mixed cases, the sedimentation rate is also abnormal, with but few exceptions, in the neural and, to a less extent, in the tuberculoid type of the disease

Even in patients with arrested leprosy of long duration, the test seldom is within the normal level

Single sedimentation tests are of no practical value in leprosy, but repeated tests at six month intervals may indicate the trend of the disease and are of some prognostic significance

At the National Leprosarium changes in the erythrocyte sedimentation index have been of slight clinical value as an estimate of the patient's reaction to any therapeutic measure

It is found convenient to divide the sedimentation tests into five zones of activity and the serial sedimentation record of each patient into horizontal, irregular, ascending and descending curves, which carry different prognostic significance

Although no claim is made that the factor responsible for the sedimentation of the erythrocytes is related to the globulin content of the blood, it is found that there is some correlation between the two conditions in patients who have leprosy

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## SYNCOPE ON EXERTION: RELATIONSHIP TO CORONARY ARTERY DISEASE\*

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THE physician, realizing that syncope is most commonly not cardiac in origin, often gives it little weight in cardiac diagnosis, unless bradycardia or extreme tachycardia is present. Relationship to physical effort is an additional circumstance which should particularly draw attention to the heart for an explanation.

The term *syncope* implies loss of consciousness due to cerebral ischemia. The essence of such an attack, ischemia, implies an inadequate flow of blood to the brain and one would look for an explanation, according to Lewis,<sup>1</sup> in a deficient input of blood into the heart, of vascular origin, *precardiac* in the sense that some mechanism interferes with blood flow to the heart, or as the result of the failure of the heart to do its work adequately, a *cardiac* cause. To these possibilities and of great interest, especially from the standpoint of mechanism, must be added a third type, a temporary cerebral ischemia due to causes for impaired cerebral flow in the arterial tree peripheral to the heart, a *postcardiac* mechanism in that blood flow is disturbed after an adequate supply leaves the heart. Under such circumstances the explanation for cerebral ischemia is not always immediately evident, and in some instances of syncope of the postcardiac type ischemia is not the apparent cause.

The three groups thus divided upon the basis of mechanism would appear at first to solve the problem of differential diagnosis and separate syncope of heart disease from other types. Unfortunately, heart disease may be responsible for the vascular, or precardiac, type, as in the syncope associated with shock in myocardial infarction, as well as for the second and third varieties. Nor is it satisfactory to know simply whether syncope comes about or does not come about from heart disease, for the diagnostic implications and therapy depend as well upon the mechanisms.

In the precardiac type of syncope, a diminished supply of blood is presented to the heart. The following case report is a rather unusual example of this group.

*Case 1* A G, age 21, presented himself for examination because of attacks of syncope. These were preceded by vertigo and occurred chiefly on changing from the recumbent to the upright position. These attacks began six months before the initial examination and were associated with general weakness, loss of libido and constipation. The patient attributed his complaint to a severe bout of influenza which necessitated a prolonged period of rest in bed.

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Physical examination was entirely normal except for drop in blood pressure on sitting and standing. Blood pressure level when lying down was usually about 120 mm Hg systolic and 84 mm diastolic, on sitting, the pressure dropped to 90 mm systolic and 60 mm diastolic, and on standing to 60 mm systolic with a diastolic level which could not be determined. With the change in blood pressure there was no remarkable change in pulse rate. The ability to perspire was apparently normal. Repeated examinations revealed the same findings.

The patient was placed on ephedrine, 25 mg four times a day, with no apparent effect until one week had passed, when gradual continuous improvement started.

In general, in the precordial variety pallor is a prominent finding. Characteristically in such episodes the patient is sitting or standing. Premonitory symptoms usually usher in the attack. The patient may fall heavily or gradually slip into the recumbent position. Emptiness in the epigastrium and nausea may develop before consciousness is lost. Both blood pressure and pulse fall, the first from vasodilatation, the second from vagal stimulation. Later the pulse may become rapid, unlike the pulse findings in the above case report. Facial pallor appears. Bursts of sweating develop. With unconsciousness the pupils dilate and the body becomes flaccid. Respirations are slow and deep.

This is the most frequent type of fainting and most commonly results from disturbances which are not serious, disturbances which brand syncope as a symptom usually of little importance as far as organic disease is concerned. Here, besides the fainting of postural hypotension, exemplified by Case 1, syncope associated with infections, stuffy environment, fasting, emotional distress, severe pain, and the like, must be placed. Further discussion of the general classification of syncope may be found in a recent report.<sup>22</sup> Syncope associated with serious disease, either vascular or non-vascular, may also fall into this group. Hemorrhage, shock pictures associated with coronary thrombosis or other disease, pain of renal or other varieties of colic, are such examples. The peripheral type of hyperactive carotid sinus reflex also falls into this group. This will be discussed further below.

These attacks usually last several minutes but may last up to 30 minutes and the patient may not develop his feeling of wellbeing for several hours. There is no particular relationship to effort or exertion, which, except in hemorrhage, would tend to encourage venous return. In postural hypotension the episodes may be repeated by changing the patient's position and confirmed by recording of blood pressure levels with the patient lying, sitting, and standing. The entrance of the carotid sinus into the episode may be tested by digital pressure over the sinus.

Syncope related to peripheral shock with serious disease is exemplified in the patients with coronary thrombosis recently reported by Coolson.<sup>2</sup> He found among 200 patients with acute cardiac infarction syncopal or epileptiform attacks in 15. Syncope occurred in 10 at the onset in the presence of apparently severe peripheral circulatory failure. In some, and particularly

those with syncope in the course of the infarction, abnormal rhythms were noted. In coronary occlusion it must also be noted that in certain instances arteriosclerotic disease probably has already impaired to some degree the cerebral circulation. In Cookson's 10 patients with syncope at the onset, five were 70 or more years old.

Syncope of the second type, resulting from impaired ability of the heart to pass on the blood presented to it is well known but not frequent in occurrence. The following case report exemplifies this group.

*Case 2* S. S., a 44 year old housewife, complained of rapid heart action accompanied by episodes of vertigo, weakness and syncope. She had been suffering from these symptoms for several years with episodes occurring as frequently as three times a week. Their usual duration was about 10 to 20 minutes. Between the attacks she felt quite well and had no symptoms of any kind.

Physical examination disclosed little of importance. Blood pressure was 138 mm Hg systolic and 80 mm diastolic, pulse 80 per minute, respirations 18 per minute. Her fundi were normal. Thyroid was not palpable. Heart and lungs showed no remarkable findings.

Laboratory data were of no importance. The basal metabolic rate was +6 per cent. Roentgenographic examination of the heart disclosed borderline figures with a transverse diameter of 14.3 cm and the internal diameter of the chest 29.2 cm. Electrocardiograms obtained during the episodes showed evidences of a flutter mechanism with 2:1 ventricular response at a rate of 130, while at other times particularly when vertigo and syncope were in evidence, tachycardia with a rate of 240 per minute in which one could not distinguish auricular flutter from paroxysmal tachycardia was present.

Treatment with digitalis and quinidine directed at the control of these symptoms was successful in markedly reducing the frequency of their occurrence.

Borg and Johnson<sup>3</sup> have discussed the differential diagnosis of syncopal attacks of this type. Two causes are given for the arrest in blood flow, one ventricular slowing or standstill, and the other ventricular tachycardia. In the former, cerebral blood flow is impaired by infrequency of ejections by the heart, in the latter, the rapid action of the heart makes it inefficient as a pump and cardiac output is markedly diminished. Coronary occlusion, especially of the right coronary artery, at times interferes with the circulation to the His bundle and produces some degree of heart block. Stokes-Adams syndrome occasionally develops in this way. Rapid ventricular tachycardia 1:1 flutter, transient ventricular fibrillation, are examples of the second type. Comeau<sup>4</sup> believes that some episodes of syncope associated with auricular fibrillation arise on the basis of ventricular standstill with the onset of the mechanism rather than on the basis of the rapid mechanism itself.

The clinical picture of cardiac syncope differs from that of the precardiac type. The disturbances in rhythm already mentioned are found. Sweating is not an outstanding feature, but convulsions often are. When heart block is the cause, one may find some degree of heart block between attacks as well.

The postcardiac type implies a disturbed circulation somewhere between the left ventricle and the cerebrum. This picture varies and at times is



difficult to differentiate from epilepsy, as exemplified by Pal's crises and certain phases of hypertensive encephalopathic syncope, which fall into this group. Here too fall certain instances of syncope on exertion associated with heart disease.

*Case 3* A. B., age 60, entered the hospital with complaint of ease of fatigue. History disclosed that on several occasions he had had loss of consciousness for a few moments while suddenly exerting himself.

Examination disclosed moderate generalized arteriosclerosis with no remarkable cardiac findings. The heart was not enlarged. There were no murmurs, the rhythm was regular, and the electrocardiogram was entirely normal. The eye grounds showed moderate arteriosclerosis.

Laboratory data, including blood count, Wassermann reaction and urinalysis, disclosed nothing abnormal. While ambulatory in the hospital the patient suddenly exerted himself in running down the hall and fainted. The episode lasted about five minutes, during which time blood pressure was normal, 124 mm Hg systolic and 68 mm diastolic, pulse was normal, 84 per minute, and respirations were 18 per minute. Electrocardiograms taken following this episode were similar to those taken before the attack and disclosed nothing abnormal.

Similar episodes were not repeated during the hospital stay and were not reproduced by digital carotid sinus stimulation.

*Case 4* G. T., age 59, white male, was brought to the hospital complaining of precordial pain of 30 minutes' duration. The pain was described as heaviness in the retrosternal region and radiated to the left arm. The patient stated that with the onset of the pain he had fainted. Episodes similar to this had been present for several years, the first attack having occurred while he was plowing. Precordial pain developed, and in a few seconds syncope appeared. The patient recovered in what he estimated to be about 10 minutes and continued with his work. On several occasions since that time similar episodes had been experienced. On admission to the ward of the hospital the patient was free of pain. However, the next day he again experienced precordial pain associated with syncope which lasted about five minutes. During this time no electrocardiogram was taken, but the pulse was found to be regular and equal to the heart rate at a frequency of 80 per minute. Blood pressure was 130 mm Hg systolic and 72 mm diastolic and unchanged.

Further examination disclosed moderate peripheral arteriosclerosis with moderate arteriosclerotic changes in the eye grounds. Examination of the heart showed no enlargement. There was a soft, systolic aortic murmur which could be heard in the neck in expiration. The carotid sinus reflex was not hyperactive when tested.

Fluoroscopic examination of the heart disclosed no enlargement or dilatation of the aorta and no evidences of calcification of the aortic valve. There were no other remarkable findings. Electrocardiogram, temperature, sedimentation rate, and leukocyte count remained normal. In the absence of evidence of coronary occlusion the patient was discharged from the hospital with a diagnosis of angina pectoris and syncope on exertion.

As shown by these cases, the heart rate continued in the usual range. Blood pressure was not remarkably depressed and no particular change in color occurred. These findings clearly differentiate the syncope from both the precardiac and cardiac types. Although the relationship of syncope to cardiac manifestations is clear-cut in Case 4, in Case 3 no cardiac manifestation accompanied the attacks and coincidental disease, epilepsy, for

example, might be suggested. However, here also the relationship of syncope to exertion is definite, a finding which sets these pictures both aside as distinct and unusual entities. Whereas Cases 1 and 2 merely represent examples of those particular types of syncope, both Cases 3 and 4 deserve reporting because of their similarity to the unusual patients described by Gallavardin (*vide infra*).

Convulsive seizures may occur, an uncommon finding in the precardiac variety. This was not shown by our cases. Ferris et al.<sup>5</sup> found in a study of the carotid sinus reflex that the clinical manifestations of fits and syncope cannot be rigidly separated.

It is apparent that organic cardiac disease may be associated with syncope due to the precardiac, cardiac, or postcardiac mechanisms. Likewise, all three mechanisms may come into play in the absence of organic heart disease. This is exemplified by the carotid sinus syndrome in which three main types of cardiovascular reaction have been observed.<sup>6</sup> A marked fall in blood pressure may develop without remarkable cardiac slowing. Secondly, asystole, or sudden slowing of the pulse may account for the symptoms, and, thirdly, symptoms, including syncope, may be associated with paling followed by intense flushing of the face *without* slowing of the heart or a fall in blood pressure. This third group is an important one because there is no striking change in the general circulation, findings which brand the syncope as a postcardiac phenomenon. Weiss and Baker assume the fainting to be due to sudden changes in cerebral vessels from carotid sinus stimulation. The three types of carotid sinus syndrome exemplify the precardiac, cardiac, and postcardiac varieties of syncope. The terms, depressor, vagal, and cerebral, applied to the carotid sinus syndrome are not satisfactory in the general classification of syncope for the cardiac variety is not usually vagal in origin and the precardiac type may not be depressor.

Although the association of syncope with heart disease usually brings to mind the cardiac variety described above as associated with mechanisml disturbances, the association, in the absence of mechanisml disturbances, of syncope on exertion with heart disease has been given little attention in the literature. Congenital heart disease, particularly with hypoplasia of the aorta, aortic regurgitation and congestive heart failure, especially with pulmonary edema and cardiac asthma, are occasionally accompanied by syncope on exertion, but not as strikingly as angina pectoris and aortic stenosis. White<sup>7</sup> indicates that syncope is uncommon in angina pectoris but that in association with vertigo it occurs occasionally. He does not mention relationship to effort but this may be implied in angina pectoris. Chief interest is seen in the French literature where Gallavardin's reports have been stimulating. In 1922, he published a report<sup>8</sup> in which syncope was associated with auriculoventricular dissociation but in 1928<sup>9</sup> he also recorded a case in which there was a normal cardiac rhythm and aortic stenosis. More recently<sup>10</sup> he described two patients with syncope on effort.

In both instances evidences of aortic stenosis were present. Others have described similar cases<sup>11, 12, 13</sup> in which syncope produced by effort was an outstanding feature, and in each an aortic lesion was present. Associated anginal pain is described. Gravier's patient had a normal mechanism during the attacks. Halbron, Lenormand and Poncet found in their cases that auriculoventricular dissociation did not explain the syncope. Syncope lasted 15 to 20 minutes, too long for Stokes-Adams attacks and for ventricular standstill also. They, too, observed an unchanged pulse rate during an episode. In both our patients syncope was present when normal heart rates were present, although no confirming electrocardiograms were taken during the attacks. It appears that cardiac syncope does not explain these episodes, although one could postulate a failure of cardiac output to accompany the needs for blood on exercise.

The association with aortic stenosis of a train of symptoms including vertigo, weakness, precordial pain and, at times, sudden death, as well as syncope, is well known in the American literature, but little is said of the relationship of syncope to exertion. Willius,<sup>14</sup> in a study of 96 cases, found that 21 per cent had anginal pain. McGinn and White<sup>15</sup> found syncope in 22 per cent of their series and angina pectoris in 19. Also little is said of the association which exists between the cerebral manifestations and coronary pain.

The mechanism of these symptoms in this disorder has never been adequately worked out. Contratto and Levine,<sup>16</sup> in a study of postmortem material in 53 cases of aortic stenosis, found calcification limited to the aortic valve and not involving the coronary orifices. In two young patients the coronary arteries appeared normal and in other subjects there were minimal atheromata. They suggested that the deformity of the valve itself was in some way responsible for this complication, whereas others<sup>17</sup> believe it due to narrowing of the aortic valve. Autopsy material indicates clearly<sup>18</sup> in some of these individuals a pathologic process in the aortic valve not in close association with the coronary orifices. The aortic regurgitation often present does not seem responsible. LaPlace<sup>19</sup> found the degree of regurgitation, as judged by the diastolic pressure, showed no relationship to the occurrence of angina pectoris. Also angina pectoris occurs in aortic stenosis without regurgitation. Other explanations include a discrepancy between coronary circulation and cardiac work and the suction principle in which the abnormal aortic valves do not cover or protect the coronary ostia and presumably blood is allowed to be withdrawn from the coronary arteries.<sup>19</sup>

Marvin,<sup>21</sup> in his interesting report on this problem, concluded that syncope and other cerebral manifestations might be based upon activity of the carotid sinus. The reflex is often hyperactive in sclerotic subjects, particularly after digitalization. French reports<sup>2</sup> also favor some type of nervous mechanism. Observations already noted in the literature and confirmed in our patient indicate that the precordial and cardiac types of reactions do not explain those instances in which a full regular pulse without

slowing was noted. The postcardiac, or so-called cerebral, type of carotid sinus reflex, in which a vascular disturbance rests upon stimulation of cerebral vessels independently from vagal slowing and the peripheral vascular effects, although the most uncommon type of reaction, can possibly explain these pictures. Weiss and Baker suggested anoxemia as a cause of fainting in the cerebral type. Ferris, Capps and Weiss have found changes in the spinal fluid dynamics associated with fainting following carotid sinus pressure which, to them, strongly suggested that variations in the caliber of the cerebral vessels frequently occur, but they showed evidence that the change in cerebral vessels is not the actual cause of fainting but merely a concomitant manifestation.<sup>5</sup> There are a number of facts which speak against the postcardiac type of carotid sinus mechanism entering into these pictures. In some of the reported cases syncope lasts longer than the one to three minutes described by Weiss et al.<sup>20</sup> In addition, with the cerebral type of carotid sinus reaction, no particular relationship to exertion has been found, a striking fact in ours as well as in the reported cases. Contratto and Levine, in 19 patients with aortic stenosis, found two with a clear-cut history of syncope but could find no positive results with carotid sinus pressure although they do report two patients without syncope but with both aortic stenosis and a definitely positive reaction to carotid sinus pressure. Furthermore, in our two patients digital stimulation of the carotid sinus produced no abnormal response.

As already stated, attempts to explain both the syncope and anginal pain have not been satisfactory. That both occur in aortic stenosis is so well known that one would suspect this diagnosis with their presence. This is also true when the syncope is related to exertion in the several instances reported in the literature. In both of our patients clinical means, including fluoroscopy, did not permit the establishment of the diagnosis of aortic stenosis, and, since both patients are still living, autopsy confirmation is not possible. The usual absence of syncope on exertion in simple coronary arteriosclerosis would lead one to believe that an additional factor, perhaps aortic narrowing, without adequate diagnostic criteria, was present. The fact remains that with or without aortic stenosis attempts to explain both syncope and anginal pain have not been fruitful. Severe pain, whether related to the heart or not, is known to be sufficient to excite the precardiac type of syncope. In the instances herein reported, as well as in some of those in the literature, precardiac syncope did not occur and also there has been no correlation between severity of pain and syncope. In fact, some of the patients developed syncope with little or no pain, as did our Case 3, and in some instances pain has not appeared until consciousness is regained. Severe anginal pain commonly occurs without syncope. Indeed, attempts to explain angina pectoris and syncope on the same grounds meet with difficulty. At times it has been reported that both syncope and angina may be relieved or prevented by nitroglycerine. Exertion to be sure may precipitate each. However, syncope often outlasts the time interval over which angina usually

lasts. Syncope lasting over half an hour has been described in some instances.<sup>21</sup> In Gupta's patient the occurrence of syncope of two hours' duration with pain on recovery of consciousness speaks against angina pectoris.

Our willingness to rule out cardiac and precardiac syncope as the types occurring in certain patients with angina pectoris or aortic stenosis certainly does not indicate that these types of syncope cannot and do not enter into the clinical picture in some instances. Nor does our evidence rule out the possibility that at times the carotid sinus reflex may play a part in these pictures, particularly as a cause of sudden death in some patients. However, in our patients and in several already referred to from the literature these mechanisms do not appear to be active.

### SUMMARY

Syncope may be classified into three types, depending upon the mechanism of its production. For a general clinical classification the terms, precardiac, cardiac and postcardiac, have been suggested. The clinical manifestations usually permit recognition of the mechanism involved, a satisfactory classification of the patient, and lead to a more rational approach to therapy.

The relationship of syncope on exertion to cardiac disease has been emphasized and two case reports illustrating this unusual manifestation are added to the several in the literature. The diagnostic value of syncope on exertion is pointed out.

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# CALCIFIC AORTIC VALVE STENOSIS: A CLINICO-PATHOLOGIC CORRELATION OF 22 CASES \*

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THE importance of calcific aortic valve stenosis is manifest when one considers that it occurs in any age group, produces symptoms which are not common to other valvular lesions and may result in sudden death without previous cardiac decompensation. Too frequently the lesion at autopsy has been entirely unsuspected. Symptoms of cardiac disease may be absent despite marked valvular stenosis and postmortem evidences of valvular disease of long duration.

This condition has been known to pathologists as calcareous or calcified aortic valve stenosis, calcific sclerosis of the aortic valve, atherosclerotic calcification of the aortic valve, calcific nodular valvular sclerosis, Monckeberg's annular or aortic sclerosis and primary ascending sclerosis of the aortic valve. Although accurately described by Monckeberg<sup>1</sup> as far back as 1904, its only interest was as an occasional postmortem finding.

It is hoped that this study, through the close correlation between clinical and pathological material, may shed some light on the diagnosis of this lesion, its genesis and insidious development, and the reasons for the failure to recognize it during the life of the patient.

## MATERIAL FOR STUDY

Twenty-two autopsied cases of pure calcific aortic valve stenosis were available for study. This represented a consecutive series of cases found at the autopsy table at Kings County Hospital from 1934 to 1942. They were carefully selected on the basis of calcareous infiltration of the aortic valve leaflets only, in the absence of significant degrees of involvement of other valves. The very occasional occurrence of very small atheromatous plaques or thickening of the mitral valve leaflets was disregarded since they were minimal and occurred not more frequently, nor to any greater degree than was observed in apparently normal hearts of persons of corresponding ages. Cases with other valvular defects were carefully avoided so that only the effects of a pure aortic stenosis on the size and weight of the heart, symptomatology, physical findings, electrocardiogram and on the production of other confusing murmurs could more clearly be defined and evaluated.

*Clinical Diagnosis.* Diagnostic criteria consist of the history, characteristic pulse, palpable thrill over the base of the heart, loud rough systolic murmur at the base of the heart or entire precordium heard loudest over the aortic valve, decreased intensity or absence of the second aortic sound and cardiac

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hypertrophy Visualization by fluoroscopy, occasional demonstration on the roentgenogram and electrocardiographic changes are helpful laboratory aids

### SYMPTOMS

*1 Symptoms of Left Ventricular Failure* These are usually the first evidence that the patient is suffering from heart disease They are exertional dyspnea, paroxysmal nocturnal dyspnea and orthopnea In our series they occurred 17 times (77.3 per cent) This may be followed by the usual signs of right ventricular failure Varying degrees of ankle swelling were mentioned 11 times (50 per cent)

*2 Angina Pectoris* Precordial pain was reported nine times (40.9 per cent) It occurred despite normal or only slightly diseased coronary arteries Such pain rarely occurs with mitral stenosis or aortic insufficiency unless the coronary ostia are damaged Precordial pain is a frequent accompaniment of aortic valve stenosis, but is sometimes caused by coronary sclerosis Some attribute it to a concomitant aortic insufficiency Contratto<sup>21</sup> and Levine<sup>5</sup> are of the opinion that the pain is due to myocardial ischemia caused by suction of blood from the coronary arteries by the accelerated blood flow

*3 Dizziness* This symptom was noted seven times (31.9 per cent) Dizziness is due to a transient cerebral anemia caused by an insufficient aortic output In some instances it may be due to hyperactive carotid sinus reflex or both factors may be involved

*4 Syncope* Attacks of syncope were noted only once (4.6 per cent) It is possible that a larger percentage could have been elicited with more thorough interrogation The explanation for these attacks is similar to that of the dizziness

### PHYSICAL FINDINGS

*1 Systolic Aortic Murmur* A systolic murmur that is confined to the aortic area is almost without exception indicative of disease of the aorta or aortic valves, namely, aortic stenosis, aortic sclerosis or aortitis, whereas a systolic murmur that is audible in the pulmonary area is of little significance This fact is important since Wilhus<sup>15</sup> found that many patients who presented an aortic systolic murmur were accepted for active service during the first World War, but on examination 15 to 20 years later all exhibited well-marked calcareous stenosis of the aortic valve The murmur may be heard over the entire precordium and is transmitted to the neck, but it is loudest over the aortic area The presence of such a murmur was discovered in only 16 cases of the present series (72.8 per cent) However, though the murmur was present, the diagnosis of an aortic stenosis was not made in five of these cases (31.3 per cent) Among possible reasons for this error were the misinterpretation of the murmur, the confusion due to the presence of other murmurs, and the absence of corroborative findings such as systolic thrill or absence of the second aortic sound



2 *Aortic Thrill* This was present only six times in all the cases (27.3 per cent). Its occurrence in the 16 patients who had an aortic systolic murmur was only 37.5 per cent. The best way to palpate the thrill is to place the palm over the aortic valve with the patient leaning forward slightly during full exhalation.

3 *Other Murmurs* The presence of other murmurs was noted 16 times (72.8 per cent). In view of the fact that our pathologic material was carefully selected for absence of other valvular involvement, reasons were sought for their occurrence and especially because of confusion in the clinical diagnosis and evaluation.

It was not uncommon to find an associated soft, low-pitched murmur of aortic regurgitation. Like the aortic systolic murmur and thrill, it is more easily heard following exercise, while leaning forward and during expiration. Despite the presence of a diastolic murmur in nine of our cases (40.9 per cent), there was no dynamically significant insufficiency and the peripheral phenomena of aortic regurgitation were almost always absent. Two of these cases had positive Wassermann reactions and presented signs clinically suggestive of an insufficiency, but the pulse pressure was small.

Apical murmurs were heard in 16 cases (72.8 per cent) despite normal mitral valves. They were variously described as soft, loud or rough. The presence of a systolic murmur at the apex has two possible explanations. Either the maximum intensity of the murmur of aortic stenosis was mistakenly placed at the apex or a relative mitral insufficiency was present due to dilation of the left ventricular chamber (cases 1 to 7 inclusive, 9 to 13 inclusive, 15 and 22). A presystolic apical murmur may be explained on the basis of an Austin-Flint murmur due to aortic regurgitation (cases 6, 7 and 11). A diastolic murmur at the apex may be due to transmission from an insufficient aortic valve (cases 5, 10, 16, 20, 22).

4 *Second Aortic Sound* Although it is usually described as absent or diminished with increasing stenosis, it was found to be completely absent only twice in our series (9.1 per cent). Varying degrees of diminution of intensity were not noted.

5 *Blood Pressure* The blood pressure usually reflects the palpatory characteristics of the pulse. Unless there is a concomitant hypertension the systolic pressure is not elevated or only slightly so, or it may be lowered. Diastolic pressures are decreased or normal, resulting in a pulse pressure that is often normal or decreased. However, when the aortic regurgitant factor is present and marked in degree the pulse pressure may be increased.

In our series, the highest systolic pressure (with one exception of 220 mm.) was 174 mm. and the lowest was 90 mm., with an average of 140 mm. of mercury. The diastolic pressures ranged from 30 to 120 with an average of 77 mm. of mercury. The average pulse pressure was 63 mm. of mercury. The higher pulse pressures were due to the frequent presence of a concomitant hypotension or of aortic regurgitation.

*6 The Pulse* The radial pulse of aortic stenosis is classically described as "rarus, parvus, tardus et longus" There is a definite halt in the rise of pressure in the radial pulse as determined by the radial sphygmogram or expert palpation in severe cases This causes the principal peak to occur later in the cycle than normally Recently, Dow<sup>22</sup> has shown experimentally that stenosis so reduces the violence of the systolic discharge that standing waves are not set up and the peripheral pulse reproduces the central pulse form with almost complete faithfulness The stenosis offers so much resistance to flow during mid-systole that the central pulse itself assumes the anacrotic and tardus characteristics

The pulses in our series were variously described as regular but weak, fair quality or volume, poor volume, rapid and small, and in three cases with regurgitant factors of the Corrigan type The classical description was not noted in our series However, it must be remembered that other factors may have influenced the plateau pulse These were age, hypertension, arteriosclerosis and aortic insufficiency Even sclerotic changes in the radial artery made detection difficult

#### LABORATORY AIDS

*1 Roentgenographic and Fluoroscopic Examination* The roentgenographic and fluoroscopic diagnosis of calcium deposits in the valve leaflets by special technic has been amply described<sup>23</sup> In 36.4 per cent of our series (approximately the figures of Dry and Willis<sup>16</sup> — 35 per cent) diagnosis based on history and physical findings was confirmed by autopsy They have demonstrated that the frequency of identification may be almost doubled (64 per cent) by the additional fluoroscopic demonstration of calcification of the aortic leaflets or annulus Arteriosclerotic dilation of the aorta may be differentiated by roentgenographic demonstration of the dilatation and calcific plaques in the aorta rather than calcification in the region of the valve

*2 Electrocardiography*<sup>16, 24, 25</sup> Left ventricular strain was evidenced by left axis deviation and T-wave negativity in Lead I or Leads I and II The presence of this additional T-wave negativity (also may be diphasic) is proof of greater left ventricular strain than left axis deviation alone This is important, since in cases in which aortic stenosis exists alone the stress is borne principally by the left ventricle In aortic insufficiency hypertrophy of all the cardiac chambers may ensue When mitral stenosis and other lesions exerting strain on the right ventricle coexist this chamber hypertrophies and both sides of the heart participate in varying degrees in sharing the abnormal strain Hence, when right ventricular strain exists other valve involvement, pulmonary artery atherosclerosis, overdigitalization, or infarctions (producing T-wave depression) must be looked for

Electrocardiographic studies made in 10 cases of our series showed a left axis deviation in all but two of the cases (80 per cent) The T-wave in

Lead I was isoelectric, negative or diphasic in all but one case. Another case with rheumatic etiology presented both complete heart block and left bundle branch block. Auricular fibrillation and pulsus bigeminus occurred once each. The heart rates ranged from 40 to 115 with an average rate of 91 per minute.

### PATHOLOGIC LESIONS OF AORTIC VALVE

The lesion of calcific aortic valve stenosis is characterized by a tendency to hyalinization of the connective tissue, depositions of lipid material in the aortic valve ring and in the aortic valve and subsequent calcification of the affected tissues. Clawson et al.<sup>4</sup> found calcium by gross examination in 84 per cent of all non-syphilitic deformities of the aortic valve. Willius and Dry<sup>14</sup> found no instance of stenosis unassociated with some calcium deposit. Detailed histopathologic investigations by Sohval and Gross<sup>15</sup> offer evidence that a primary degenerative disease of the valve may be differentiated from those caused by rheumatic fever. Essentially, calcification in the former begins at the base of the valve and affects the fibrous portion of the valve on the aortic surface, whereas the latter occurs in the distal third involving the spongiosa and ventricularis layers on the ventricular aspect of the aortic cusps.

In addition, they demonstrated that healed rheumatic deformities could be found in various significant sites, i.e., left auricle, valve rings and valve cusps, pericardium and several valves may be affected. The degree of calcification closely parallels the degree of stenosis, but sclerosis of the aorta and coronary vessels is likely to occur in inverse proportion to the degree of stenosis of the aortic valve. Paralleling Cabot's early collection of autopsied cases,<sup>7</sup> a terminal acute endocarditis was superimposed on the calcified lesion three times, twice in cases of chronic rheumatic valvulitis (cases 7 and 16) and once in a patient with arteriosclerosis (case 3).

The gross lesions of the aortic valve can be characterized in one of the following ways:

1. Calcific nodules of varying sizes occur in the substance and base of the valve rather than in the free margins, thus producing a thickening of the valve. Marked deformities and stenosis result in the advanced group which may make a differentiation between a true and false bicuspid valve difficult.

2. Calcific deposits and ridges are often found in the sinuses of Valsalva. The aorta frequently remains free from atheromatous changes.

3. Calcific deposits may assume ragged, rounded or ridge-like shapes and may ulcerate through the endocardium with superimposed thrombus formation, especially in the terminal phase.

### ETIOLOGY

Although considerable controversy is still prevalent concerning the existence of certain lesser factors in the causation of calcific aortic valve stenosis,

sis, rheumatic fever and arteriosclerosis have a definitely established relationship to the condition (table 1)

1 *Rheumatic Fever* That calcareous stenosis might be of a rheumatic nature was first suggested by Christian<sup>2</sup> This view was upheld by the studies of Dry and Wilhus<sup>3</sup> and Clawson, Noble and Lufkin,<sup>4</sup> who believed it to be the only factor involved This was based upon a history of rheumatic fever, old healed defects of other valves, and the relics of pericarditis These opinions have been further corroborated by Friedberg and Solval<sup>5</sup> and especially by the excellent microscopic studies of Karsner and Koletsky<sup>6</sup> The latter found some evidence of rheumatic fever in 37 out of 40 cases

TABLE I  
Sex and Etiological Distribution

	Male	Female	Total
Arteriosclerosis	14	2	16
Rheumatic fever	4	1	5
Subacute bacterial endocarditis	—	1	1
Total	18	4	22

under study They felt that if the Monckeberg type of aortic valvular sclerosis existed, it could not be distinguished morphologically from that associated with chronic or healed rheumatic fever Delafield and Prudden<sup>12</sup> stated that among the most common and important examples of calcareous degeneration may be mentioned those which occur in the heart valves in endocarditis From a clinicopathological study of 28 cases of pure aortic disease, Cabot<sup>13</sup> also concluded that it was due to a rheumatic endocardial infection A history of rheumatic fever could not be elicited in more than 22 per cent of the cases<sup>3</sup> The remainder suffered very mild or atypical episodes which went unrecognized Clawson et al<sup>4</sup> obtained a history of rheumatic fever in 35 per cent of their series

Since our case studies were based on selected material with exclusion of associated valvular defects, it must be realized that statistically the avoidance of patients with more frequent involvement of other valves markedly depreciated the frequency of rheumatic fever as an etiological factor Most of our cases were specifically questioned concerning rheumatic episodes, and this was present in three out of five cases (60 per cent) An even greater percentage probably was not found because the infection was so mild or atypical that its true nature went unrecognized Yet, it is important to note that our cases were drawn from the Middle Atlantic States where rheumatic infections are severe The total number of cases considered to be of rheumatic origin, from history as well as pathologic findings, was only five out of 22 cases (22.3 per cent)

2 *Arteriosclerosis* Although atherosclerotic calcification of the valve was originally considered as the factor of prime importance there has been

a tendency of late to abandon this view. The objection raised to the possibility of a primary degenerative disease of the valve is that the aorta showed less or even no calcification. This is not valid, since it cannot be argued that atherosclerosis of the aorta is not degenerative because the valve is not affected. According to White,<sup>9</sup> both calcification secondary to rheumatic or other types of infectious endocarditis and primary atherosclerotic degeneration may exist together.

In our series, an arteriosclerotic factor occurred in 16 cases (72.7 per cent). No history of rheumatic fever or stigmata of rheumatic disease were revealed at autopsy in any of the cases. A past history could not be ascertained in two cases due to deaf mutism and unconsciousness. Therefore, when the aortic valve alone is involved, the arteriosclerotic factor is much more important than the rheumatic (large table). However, this probably does not hold true when other evidences of rheumatic involvement are present (mitral valve disease, pericardial disease or disease of the endocardium).

**3 Subacute Bacterial Endocarditis** The supposition that subacute bacterial endocarditis is an underlying factor has been supported by Libman,<sup>10</sup> Perry,<sup>11</sup> and others. They are of the opinion that calcification may occur as part of the healing process in subacute bacterial endocarditis after the patient becomes bacteria free. Subsequently, after months or years, there may be a reinfection of the diseased valve, usually by the *Streptococcus viridans*.

We found one such case (case 17) in our series (4.6 per cent) occurring in a 41 year old female with a cardiac history of eight years' duration. It might be argued that the subacute vegetations were superimposed on atheromatous ulcerations, rather than a healing and calcification end stage of primary subacute bacterial endocarditis. The age group in which such cases occur, however, probably precluded a primary atherosclerosis of the valve with a superimposed infection. It was difficult to state with any degree of certainty whether the calcification followed the initial rheumatic involvement or the bacterial invasion. In answer to those who consider this factor inoperative, it may be stated that since healing has been repeatedly reported in such cases, there is no reason why it should not terminate in calcification as an end result.

*4 Subacute Bacterial Endocarditis* In three of our cases (6.1 per cent) the

## History

No	Patient	Age	Sex	Past History	Dizziness	Angina	Syncope	Other Symptoms
1	C P	62	M	Negative	-	-	-	Dyspnea; Edema
2	F I	55	M	Found unconscious				
3	F J	70	M	Deaf mute				Dyspnea
4	F S	75	M	Negative	+			Edema; Dyspnea; Orthopnea
5	C J	82	F	Negative	+			Edema; Dyspnea
6	N J	25	M	Rheumatism 10 yrs	+	++++		Edema; Dyspnea
7	W H	52	M	Rheumatic poly arthritis 10 yrs with heart involvement		++++		Edema; Dyspnea
8	W I	51	M	No past history Onset present illness with pneumonia	-	-	-	Dyspnea; Cyanosis
9	H W	55	M	No rheumatic history	-	-	-	Paroxysmal nocturnal dyspnea
10	H R	58	M	No rheumatic history	+	-		Edema; Dyspnea; Orthopnea
11	J A	36	M	No rheumatic history passed influenza 9 years ago				Edema; Dyspnea
12	F I	59	M	Negative		+		Edema
13	S D	71	M	Previous attack of cardiac decompensation	+	++		Dyspnea; Edema
14	P C	80	M	No rheumatic history		-		Dyspnea; Edema
15	R W	61	M	No rheumatic history	++		++	Dyspnea
16	C F	36	F	Rheumatic heart trouble since childhood	++	++++		Dyspnea; Edema
17	F C	31	F	Cardiac for 4 yrs		++++		Dyspnea
18	F S	57	F	No cardiac history Admitted for common duct stones	-	-		
19	C B	62	M	No rheumatic history		++++		Edema; Paroxysmal nocturnal dyspnea
20	M M	72	M	Negative		++		Edema; Dyspnea
21	F S	77	M	Negative		-		Edema
22	S C	44	M	No rheumatic history		++++		Dyspnea

# Physical Findings

A D	C Murmurs	A	B P		Pulse		Cardiac Hypertrophy	Rhythm	E K G	Clinical Diagnosis	Diagnosis Correct	Duration Cardiac Illness	Duration Hospital Stay
			Syst	Diast	Type	Rate							
	Ro zh systolic at apex and base, in dec at base		130	100	Fair volume	110	+++	RSR		Arteriosclerotic heart disease with decom- pensation	No	6 mos	1 day
	Systolic at apex		160	120	Poor volume	76	-	RSR		Cerebral hemorrhage	No	?	1 day
-	Systolic at apex and base	Absent	132	70	Fair quality	81	++	RSR		Aortic valve sclerosis	Yes	4 yrs	1 yrs
	Systolic at apex and Jnd left lower cr at base		171	106	?	?	++++	RSR		Chr myocarditis, gen arteriosclerosis	No	6 mos	1 day
-	Monor syst apex and diast toic at apex		220	110	Fair volume	75	++	AF		Arteriosclerotic heart disease, gen arterio- sclerosis	No	1 yr	5 days
+	Systolic and diastolic at apex. Diast at base		150	110	Corrigun	100	++++	RSR	No axis de- viation, sinus tachycardia	Rheumatic and luetic heart disease (+++++ Wass)	Yes	3 mos	2 mos
-	Systolic and diastolic at apex		110	60	Corrigun	90	++++	RSR		Rheumatic heart dis- ease	Yes	1 yrs	2 mos
	None		92	60	Rapid irreg- ular fair quality	90	-	AF	Left axis de- viation, urtic- ular fibrilla- tion, myocar- dial fibrosis	No cardiac diagnosis, lobar pneumonia	No	3 days	9 days
+	Rough systolic at apex		119	70	Fair volume	110	+++	RSR	Left axis de- viation, myo- cardial fibrosis	Chr rheumatic valvul- ar heart disease	Yes	6 mos	2 wks
+	Is and fro at apex, heard best at base		130	65	Weak	90	++++	RSR	Left axis de- viation, myo- cardial fibrosis, pulsus bigemi- nus at times (160)	Luetic heart disease (+++++ Wass)	No	5 yrs	1 mo
-	Aortic first		140	30	Fair quality	90	+++	RSR	Left axis de- viation myo- cardial damage	Luetic heart disease (+++++ Wass)	No	3 mos	2 mos

# Physical Findings

No	Patient	Age	Sex	Aortic Systolic	Aortic Thrill	Aortic Dias	Other Murmurs	As	B P		Pulse		Cardiac Hypertrophy	Rhythm	E K G	Clinical Diagnosis	Diagnosis Correct	Duration Cardiac Illness	Duration Hospital Stay
									Sys	Dias	Type	Rate							
12	L E	59	M	++			Systolic at apex		150	80	Fair quality	100	+++	RSR	Left axis deviation	Arteriosclerotic heart disease	No	13 days	10 days
13	V D	71	M	++++	++	-	Soft systolic at apex		162	70	Fair volume	70	++	RSR		Arteriosclerotic heart disease with aortic stenosis	Yes	1 yr	17 days
14	P G	80	M	++			None		170	70	Fair volume	95	?	RSR		Hypertensive heart disease with acute myocardial failure	No	5 wks	1 day
15	R W	61	M	-	-		Systolic at apex		160	100	?	40	++	Complete heart block	Left axis deviation, complete heart block, left bundle branch block	Stokes-Adams syndrome	No	8 mos	2 wks
16	G K	36	F	++	-		Double murmur at apex		110	68	Rapid and small	120	++	RSR	Left axis deviation	Chronic rheumatic heart disease	Yes	1 yr	1 wk
17	I C	11	F	++	-		None		136	90	Weak	110	++	RSR		Subacute bacterial endocarditis	Yes	8 yrs	3 days
18	J S	57	F	-	-	-	None		135	90	?	80	+	RSR		Acute toxic hepatitis, secondary to stones	No	11 days	11 days
19	C H	62	M	-		-	None		90	65	Weak	115	-	RSR	No axis deviation, myocardial damage, sinus tachycardia	Arteriosclerotic heart disease with decompensation	No	6 yrs	1 day
20	M M	72	M	+++		++	Diastolic at apex		168	60	Corrigan	90	+++	RSR x systoles		Hypertensive heart disease with possible aortic insufficiency	No	6 wks	2 days
21	F S	77	M	++++	++	-	None	Absent	110	60	Poor volume	100	+	RSR		Arteriosclerotic heart disease with calcific aortic stenosis	Yes	Few yrs	1 wk
22	S C	61	M	++++	++	++	Double murmur at apex		110	70	?	100	+++	RSR	Left axis deviation, severe myocardial damage	Luetic aortic, coronary insufficiency (++++ Wass)	No	1 wks	13 days



# Pathology

Description of Aortic Valve	Etiology Valve Disease	Heart Weight in Grams	Cause of Death
The aortic cusps with large nodular calcified masses, attached to each of the cusps	Arteriosclerosis	650	Pulmonary edema
The aortic cusps with a stenosis admitting a lead pencil	Arteriosclerosis	550	Cerebral hemorrhage, bronchopneumonia
The fusion of the right anterior cusps involving both surfaces superimposed on a chronic stenosis with immobility and marked stenosis acute vegetative endocarditis	Arterio-sclerosis	580	Myocardial insufficiency, uraemia
The cusps are markedly inflamed and covered with many calcific nodules	Arterio-sclerosis	Much enlarged heart, cor box in sum type No weight stated	Chr myocarditis, bronchopneumonia
The cusps are moderately fused preventing	Arteriosclerosis	400	Thrombosis sup mesenteric artery, hypernephroma
The cusps are moderately fused preventing	Rheumatic fever	520	Chr myocarditis, bronchopneumonia
The cusps are moderately fused preventing	Rheumatic fever	960	Adenocarcinoma of stomach
The cusps are moderately fused preventing	Arteriosclerosis	280	Lobar pneumonia
The cusps are moderately fused preventing	Arteriosclerosis	720	Bronchopneumonia
The cusps are moderately fused preventing	Arteriosclerosis	850	Pulmonary edema
The cusps are moderately fused preventing	Rheumatic fever	700	Acute and chronic rheumatic endocarditis

# Pathology

No	Patient	Age	Sex	Description of Aortic Valve	Etiology Valve Disease	Heart Weight in Grams	Cause of Death
12	L I	39	M	Not described fully other than marked aortic stenosis and thickening	Arteriosclerosis	410	Bronchopneumonia
13	V D	71	M	Cusps are all thickened, nodular and calcified. The opening is contracted to 5.5 cm and the cusps so calcified as to be immovable.	Arteriosclerosis	610	Generalized arteriosclerosis
14	P G	80	M	Valves are markedly sclerotic and inflexible. The commissures are fused, producing a calcific stenotic lesion.	Arteriosclerosis	500	Pulmonary edema
15	R W	61	M	Cusps are fused, thickened and calcified, resulting in stenosis due to old rheumatic fever.	Rheumatic fever	420	Pulmonary edema
16	G K	36	F	Valve is markedly distorted, calcified and stenosed with superimposed friable fine vegetations. Large ulceration at base of semilunar valve. Acute verrucous endocarditis superimposed on chronic rheumatic endocarditis with marked calcific aortic stenosis.	Rheumatic fever	600	Pulmonary infarction
17	F C	11	F	Aortic valve is markedly stenosed, hardened and distorted with ulcerations at edges of cusps. Subacute ulcerative endocarditis with calcific stenosis of aortic valve and multiple embolization.	Subacute bacterial endocarditis	500	Left ventricular failure with multiple embolization
18	I S	57	F	Valve is involved by marked arteriosclerotic calcification especially at commissures with narrowing of lumen.	Arteriosclerosis	170	Acute toxic hepatitis secondary to stones
19	C H	62	M	Valve is markedly thickened and calcified with fistulomorph orifice. Only 2 cusps are distinguished with calcified nodules throughout the valve.	Arteriosclerosis	510	Pulmonary infarction
20	M M	72	M	Valve presents thickening, hardening and fusion at the commissures. No evidence of lues.	Arteriosclerosis	Markedly enlarged. No weight stated.	Bronchopneumonia
21	I S	77	M	Valve is markedly thickened, calcified, stenosed with irregular yellow white nodules.	Arteriosclerosis	580	Bronchopneumonia
22	S C	41	M	The anterior cusps are solidly fused. The posterior cusp is ulcerated at its free edge with superimposed fresh thrombi. Valves are markedly calcified, nodular and ulcerated. The calcific nodules are more prevalent at the base of the aortic surface of the valve. There is acute aortitis not involving the valve.	Arteriosclerosis	670	Pulmonary edema

when there is a positive Wassermann reaction and syphilitic aortitis. He insists that syphilitic valvulitis with stenosis of the valves does not occur and only a regurgitant lesion can be produced by syphilis. Hence, the finding of syphilitic stigmata should be regarded as a concomitant lesion.

5. *Miscellaneous Factors* Other conditions have been implicated from time to time<sup>3, 14, 15, 16</sup>. The facts and evidence in their favor have been so meager as to fail to establish them as acceptable factors. They require only the briefest mention.

(a) Cases of congenital aortic atresia have been reported in the literature in which the three leaflets persist as rudimentary ridge-like structures which are fused<sup>17</sup>. It usually occurs in association with a septal defect and may become calcified.

(b) Calcification of a bicuspid aortic valve.

(c) General toxic, distant infectious processes,<sup>18</sup> or an unidentified form of chronic inflammation.

(d) Proof is wanting for a metabolic cause of the disease.<sup>19</sup>

#### AGE AND SEX DISTRIBUTION

The greatest number of cases occurred in the age groups of 50 to 80 years. The ages ranged from 25 to 82 years with an average age of 59 years. As was to be expected, a rheumatic etiology was most marked in the younger age groups (25, 36, 36, 52 and 61 years of age respectively with an average age of 42 years). The arteriosclerotic group was composed of the following ages: 43, 54, 55, 55, 57, 58, 59, 62, 62, 70, 71, 72, 75, 77, 80 and 82 years, with an average age of 65 years.

TABLE II  
Age-Sex Distribution

Age Group	Male	Female	Total
10-19	0	0	0
20-29	1	0	1
30-39	1	1	2
40-49	1	1	2
50-59	6	1	7
60-69	3	0	3
70-79	5	0	5
80-89	1	1	2
Total	18	4	22

## CARDIAC ENLARGEMENT AND HEART WEIGHTS

Hypertrophy of the heart was due to a combination of several factors. These consisted of the mechanical obstruction of stenosis (with or without relative insufficiency) and hypertension. The reason why there were so many of these large hearts with unimpaired cardiac reserve is that the development of the cardiac hypertrophy proceeded subtly and the coronary flow remained adequate. The heart tolerates stenosis of the aortic valve far better than a mitral stenosis. Indeed, a tremendous heart may be an unexpected finding at autopsy examination.

Without corrections for obesity and hypertension, the heart weights ranged from 400 grams (with one exception of 280 grams) to 960 grams, with an average of 575 grams (table 3). This quite accurately paralleled the degree of enlargement found clinically.

TABLE III  
Heart Weights (in grams)

200-299	300-399	400-499	500-599	600-699	700-799	800-899	900-999
280	—	400 410 420 470	550 580 520 500 500 540 580	650 610 600 670	720 700	850	960

## DURATION OF CARDIAC ILLNESS

Following the onset of the first symptoms, the total duration of the illness ranged from three days to eight years (large table). It proved to be variable in all etiologic, age and sex groups. The hospital stay was more uniform and much shorter, ranging from one day to two months, with one exception of four years. The rheumatic group had a tendency to a longer hospitalization period than the arteriosclerotic group.

## CAUSES OF DEATH

The course was generally slow and progressive, the valve becoming more and more stenosed as more calcium was deposited on the leaflets. Therefore it was present for many years even without cardiac symptoms, but when congestive failure finally ensued the duration of life was short. Auricular fibrillation occurred in 14 per cent of Dry and Willis' cases,<sup>23</sup> but it must be emphasized that half of these were complicated by the involvement of other valves. Auricular fibrillation was rare when there was a left axis deviation. Solitary aortic stenosis is tolerated by the heart much better than mitral stenosis alone.

Extracardiovascular causes of death (table 4) occurred in nine cases (40.9 per cent). Of the cardiovascular causes (table 4) pulmonary edema and congestive heart failure accounted for eight cases (36.4 per cent). Vascular accidents and disease accounted for five deaths, 20.8 per cent (1 generalized arteriosclerosis, 2 pulmonary infarctions, 1 cerebral hemorrhage, and 1 thrombosis of the superior mesenteric artery). These figures are similar to those of other authors.

TABLE IV

Cause of Death	No. of Cases
Bronchopneumonia	6
Pulmonary edema	5
Congestive heart failure	2
Pulmonary infarction	2
Acute rheumatic carditis	1
Thrombosis superior mesenteric artery	1
Cerebral hemorrhage	1
Generalized arteriosclerosis	1
Lobar pneumonia	1
Adenocarcinoma of stomach	1
Acute toxic hepatitis	1
Total	22

The possibility of sudden death existed in five cases, all of arteriosclerotic origin, who were acutely ill for less than 24 hours. One could not say with complete assurance that these cases were sudden deaths rather than acute myocardial failure or massive pulmonary infarction. The occurrence of sudden death has many explanations.<sup>7, 20</sup> It may be caused by myocardial infarction due to acute coronary occlusion or coronary insufficiency, severe cerebral ischemia, cardiac standstill, ventricular fibrillation, hypersensitive carotid sinus reflex or obstructing thrombi formed on the stenosed aortic valve.

## SUMMARY

Among the reasons for the failure to make an accurate diagnosis were the misinterpretation of the murmur, the confusion caused by the presence of other murmurs and the lack of corroborative findings, such as a systolic thrill and absence of an aortic second sound. The presence of apical murmurs during systole was either due to transmission from the base or due to a relative mitral insufficiency caused by the dilatation of the left ventricle. Presystolic murmurs at the apex were of the Austin-Flint type. The pulse pressure was usually normal or decreased, but was sometimes increased because of concomitant aortic regurgitation or hypertension, although it was frequently difficult to estimate because of radial artery sclerosis. Clinical enlargement of the heart closely paralleled the weight which was increased considerably. Fluoroscopic and roentgenographic examination is capable of almost doubling the average frequency of diagnosis which was 36.4 per cent in our series. Left axis deviation and T-wave negativity were helpful in differentiating aortic insufficiency and mitral lesions since these tend to produce hypertrophy in the right chambers as well, with resultant right ventricular strain. Three types of calcification in the aortic valve have been described. In the rheumatic type, calcification began in the ventricular aspect of the distal third of the cusps, whereas, in the arteriosclerotic types it began at the base of the aortic surface. The degree of calcification closely paralleled the degree of stenosis. Cardiovascular and extracardiovascular causes of death were about equally divided, but of the former pulmonary edema and congestive heart failure predominated. The possible occurrence of sudden death existed in five cases of arteriosclerotic origin but these may have been due to acute myocardial failure or pulmonary infarction.

### CONCLUSION

In the absence of hypertension and definite mitral valve involvement, a systolic murmur at the aortic area should suggest calcific aortic valve stenosis. This possibility becomes greater in the presence of dizziness, precordial pain, regular sinus rhythm, cardiac enlargement and an absent second aortic sound. Roentgenologic and especially fluoroscopic studies, as well as electrocardiographic findings, may verify this. Many pitfalls in clinical diagnosis are evaluated and correlated with the pathologic findings. In the etiology of pure calcific aortic valve stenosis, arteriosclerosis is more than three times as important as rheumatic fever. The former factor is prevalent among males in an advanced age group, the latter among females averaging 23 years younger.

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# ANEURYSMS OF THE ABDOMINAL AORTA \*

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ANEURYSM of the abdominal aorta must be considered in the differential diagnosis of obscure abdominal disorders. Unfortunately, its identity is rarely established in the early period of development. In more advanced lesions, where only a vague mass lacking the features of vascular origin is found, it still may defy recognition. In such situations one must turn to the roentgenogram to help define the tumor and establish its character.

This report will review the available literature and add nine additional cases. In five the diagnosis was confirmed by postmortem examination. The incidence, etiology, pathology, clinical features and laboratory procedures of importance will be discussed.

*Incidence* In 1903, Bryant,<sup>1</sup> reviewing 18,678 necropsies performed at Guy's Hospital between 1854 and 1900, found among 325 cases of aortic aneurysms 54 (0.28 per cent) of the abdominal aorta. Osler<sup>2</sup> noted 60 aneurysms in the first 2,200 necropsies performed at the Johns Hopkins Hospital, of which 11 occurred in the abdominal aorta, an incidence of 0.5 per cent. Of the 18,000 necropsies studied at the same institution over a 16-year period, 16 cases of abdominal aortic aneurysms were found, an incidence of 0.09 per cent. The ratio of abdominal to thoracic lesions was one to ten. In a statistical study by Lucke and Rea<sup>3</sup> in 1921 of postmortem studies made at the Philadelphia General Hospital and the Hospital of the University of Pennsylvania reviewing the years 1875 to 1916, there were 40 cases of aneurysms of the abdominal aorta in a total of 12,000 necropsies, an incidence of 0.3 per cent. Of 321 aneurysms, 173 were in the aortic arch, 31 in the thoracic aorta and 40 in the abdominal aorta. Gernert<sup>4</sup> reviewed 1062 autopsies and found six aneurysms of the abdominal aorta in a total of 28 aneurysms of all types. Kampmeier<sup>5</sup> listed 68 cases of abdominal aneurysms reporting a ratio of 1 to 7.8 of the abdominal to the thoracic types. Saleeby and McCarthy<sup>6</sup> in a study of 84 cases of aneurysms from the surgical service of the Philadelphia General Hospital found that of 74,620 admissions in a 32 year period, 17 aortic aneurysms were encountered. Of these, 13 were located in the abdominal aorta and 33 in the thoracic aorta. In 1941 a comprehensive review of the subject by Pullin, Carthman and Wilson<sup>7</sup> included 1,000 cases of aneurysms of the aorta. Of these, 111 were of the abdominal type.

It is significant that the ratio of abdominal to thoracic aneurysms has undergone a change from 1 to 10 (Osler, 1905), 1 to 5.1 (Lucke and Rea, 1921), 1 to 7.8 (Kampmeyer, 1936) to values of 1 to 2.8 (Saleeby and McCarthy, 1938), and 1 to 3.3 (Ruffin, Castleman and White, 1941). A declining incidence of aneurysm due to syphilitic aortitis and an increasing incidence of arteriosclerotic aneurysms is suggested by these figures.

*Distribution* Abdominal aortic aneurysms occur most often in males. Bryant<sup>1</sup> noted that 90 per cent of his 54 patients were men, as were 14 of Osler's 16 cases. Keen<sup>15</sup> states that the frequency of abdominal aneurysms in the male is 11 times that in the female.

*Age* Nine of Osler's 16 cases were under 40 years of age, and in three the disease appeared before the thirtieth year.<sup>2</sup> Bryant<sup>1</sup> found that 63 per cent of his 54 patients were under 40, and two were under 20 years of age. Ruffin, Castleman and White<sup>7</sup> observed the age at death to average 46.4 years in their syphilitic patients, whereas in 23 cases described as arteriosclerosis and senile ectasia the average age at death was 72.7 years. Kampmeyer<sup>5</sup> found that 46 of his 68 cases were less than 45 years of age. There is general accord as to the age distribution of the two major groups of aneurysms, the syphilitic occurring in the fourth and fifth decades and the arteriosclerotic in the sixth and seventh.

*Etiology* The etiology of aneurysms of the abdominal aorta has been ascribed principally to syphilis and arteriosclerosis, either independently or together. Other etiologic factors include trauma, such as perforating abdominal gunshot or stab wounds, contiguous extra-arterial disease with secondary injury to the vascular wall, inflammatory vascular lesions such as tuberculosis, streptococcus infections and rheumatic fever.<sup>8, 9, 10, 19</sup> The history of a chancre and a positive Wassermann reaction assist in establishing the etiology. However, the serologic reactions may be negative in some patients manifesting evidence of syphilitic infection both grossly and microscopically.<sup>8</sup>

Syphilitic mesarteritis has been considered the primary cause of sacculated and multiple aortic aneurysms, whereas arteriosclerosis is associated with the fusiform or diffuse type. The distribution of the various aneurysms was described by Ruffin, Castleman and White<sup>7</sup> who studied 66 aneurysms in the thoracic and 20 in the abdominal aorta. Of these 66 thoracic lesions, 60 were syphilitic and three arteriosclerotic. Three were classified as senile ectasia in which dilatation of the vessel occurred without evidence of arteriosclerosis or syphilis. Of the thoracic aneurysms, 21 occurred in the ascending aorta, 37 in the arch, and eight in the descending thoracic portion. Of the 20 abdominal aneurysms, three were syphilitic and 17 arteriosclerotic in origin.

*Pathology* Aortitis is the most frequent lesion of tertiary syphilis and may be its sole manifestation.<sup>11</sup> The saccular aneurysm characteristic of the disease is the result of an inflammatory process which begins as a mesarteritis.

Microscopically, patchy areas of lymphocytic infiltration form about the vasa vasorum in the media and adventitia. Tissue destruction is rapid and the dissolution of normal architecture, which is more profound than in arteriosclerosis, results in scarring and subsequent ectasia. A fibrous adventitia of varying thickness eventually forms the aneurysmal wall. The sac often contains a laminated thrombus in which organization rarely occurs.

In arteriosclerotic aneurysms the arterial wall is weakened throughout because of progressive medial changes. After the elastic fibers degenerate, they are replaced by fibrous hyaline tissue, a non-inflammatory process in which the change progresses from the intima to the adventitia. The extent of this replacement has been evaluated by Krafka<sup>9</sup> who found a loss of 70 per cent of the aortic elasticity in elderly patients because of degenerative changes. In arteriosclerosis these changes progress from intimal thickening to the deposition of atheromatous plaques which may eventually ulcerate. The media is slowly replaced by connective tissue leaving a thickened, sclerotic adventitia as the sole supporting structure. The progressive dilatation of the vessel as a result of these changes reflects its inability to resist intravascular tension.<sup>10</sup>

Dilatation of the aneurysm from the constant strain may eventually terminate in rupture at a point near the origin of the sac at the aorta, an area of minimal resistance.<sup>12</sup> The frequency of rupture as a terminal event was emphasized by Kampmeyer<sup>8</sup> who found that 31 of 38 patients examined post mortem expired in this manner. No statistics showing the relative frequency of rupture in syphilitic as compared to arteriosclerotic aneurysms were available. Of the five aneurysms studied at autopsy in the present series, one of the two syphilitic aneurysms and two of the three arteriosclerotic aneurysms ruptured.

The site of election of abdominal aortic aneurysms is near the celiac axis. The areas just below the diaphragmatic hiatus and above the iliac bifurcation are sometimes affected.<sup>13,14,15</sup> The regions of relative weakness in the abdominal aorta exist because of the loss of diaphragmatic support immediately below the hiatus and because of the sudden alteration in blood pressure occurring near the origin of the large vascular trunks.

Erosion of the vertebral bodies occurs because of a chronic inflammatory reaction produced in the cancellous bone by the pressure of the enlarging aneurysm. The cartilage, being avascular, does not show this reaction and consequently is preserved. The crescentic shaped areas of re-absorption posterior and distal to each disk are a result of the support given to the sac by the intervertebral disc and the subsequent relief of pressure on adjoining bone (figure 1, 6).<sup>16</sup> Other suggested that the yielding nature of cartilage played

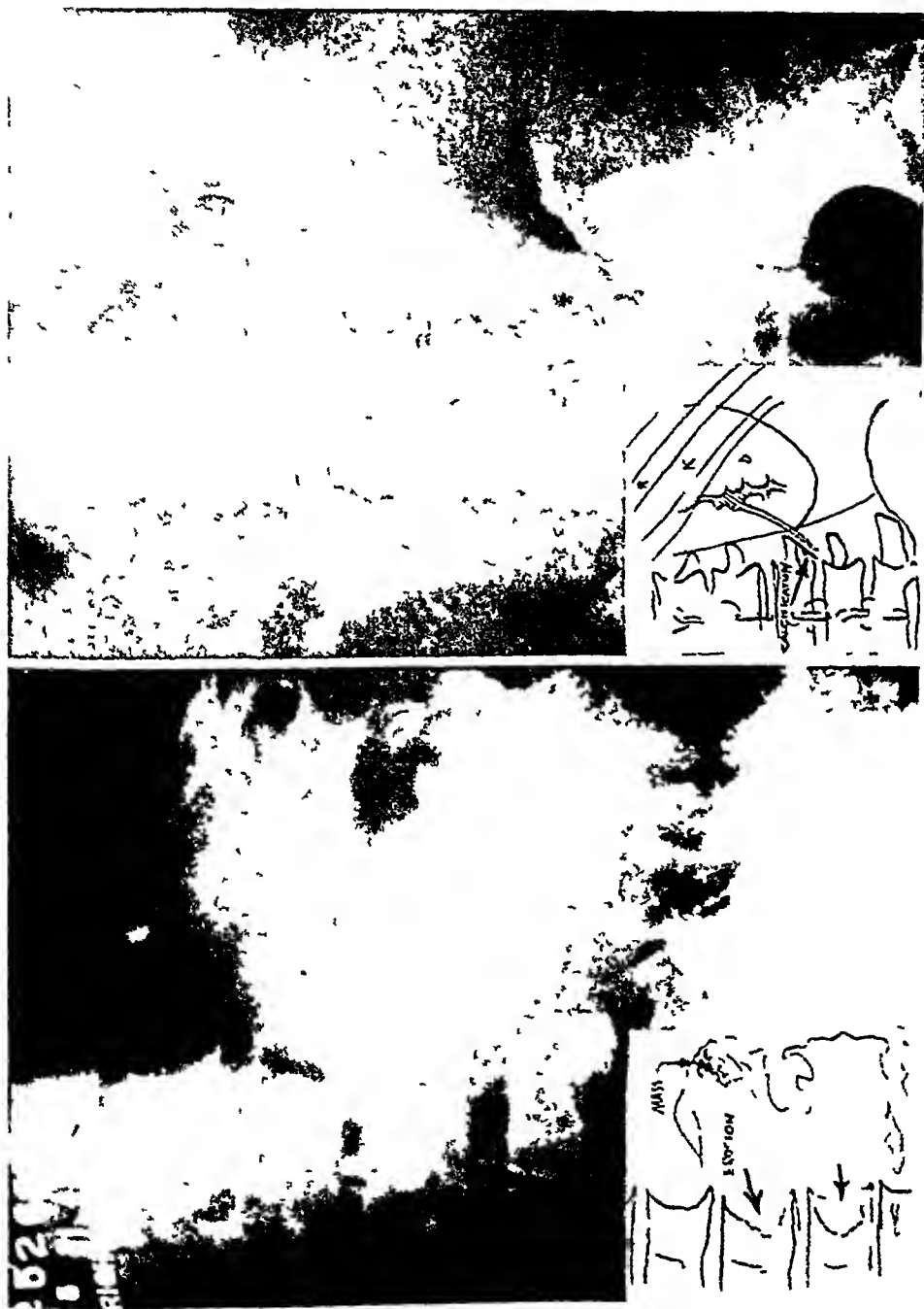


FIG. 1 Case 1 Right oblique exposure of the spine showing destruction (scalloping) of the bodies of the twelfth thoracic and first lumbar vertebrae by an aneurysm of the abdominal aorta.

FIG. 2 Case 3 Intravenous pyelogram showing lateral displacement and angulation of the right ureter at the level of the third lumbar vertebra. A linear area of calcification is seen above the site of angulation parallel and just medial to the ureter.

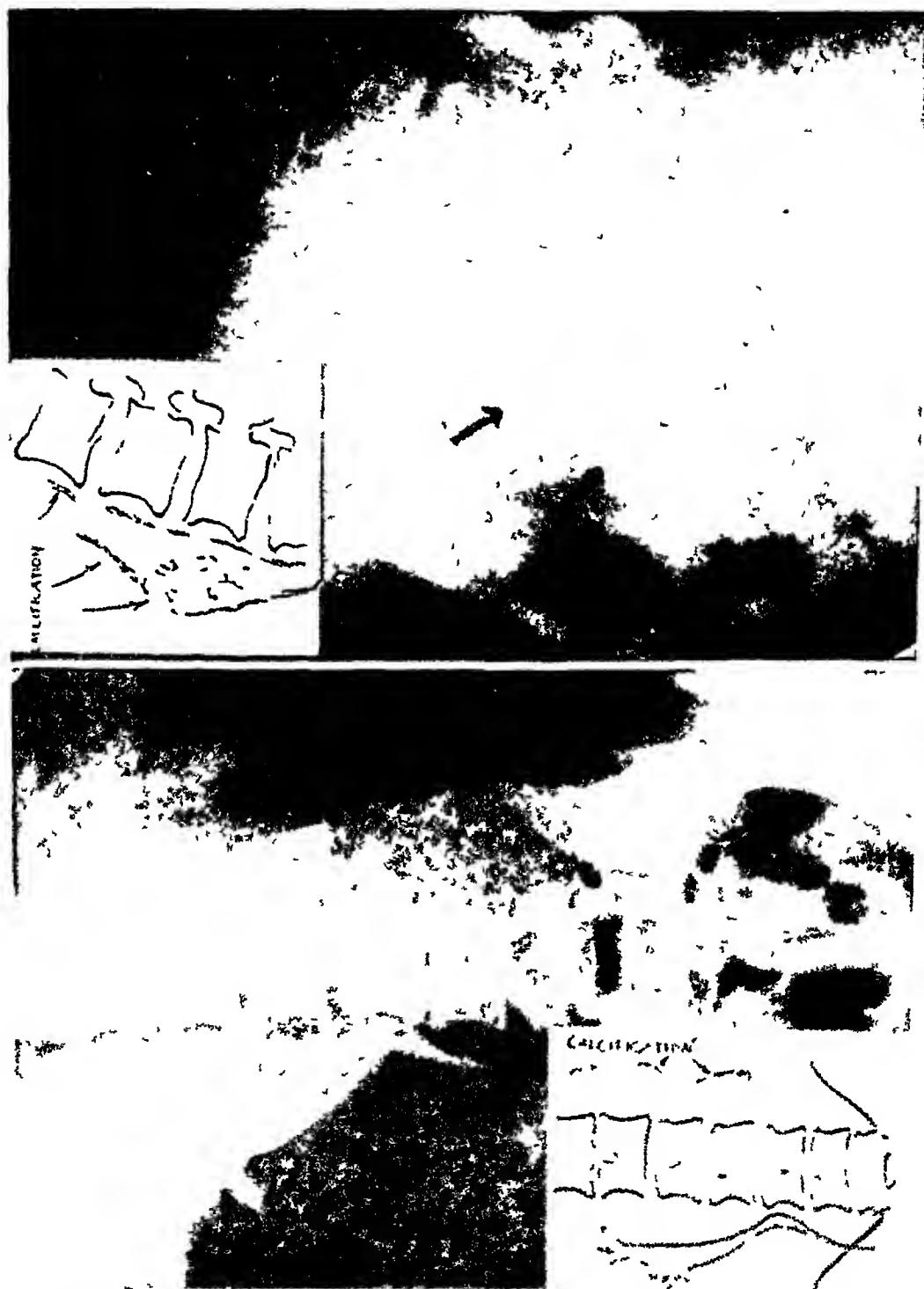


FIG. 4. Case 7. Calcification in the wall of an aneurysm of the abdominal aorta anterior to the second, third and fourth lumbar vertebrae.

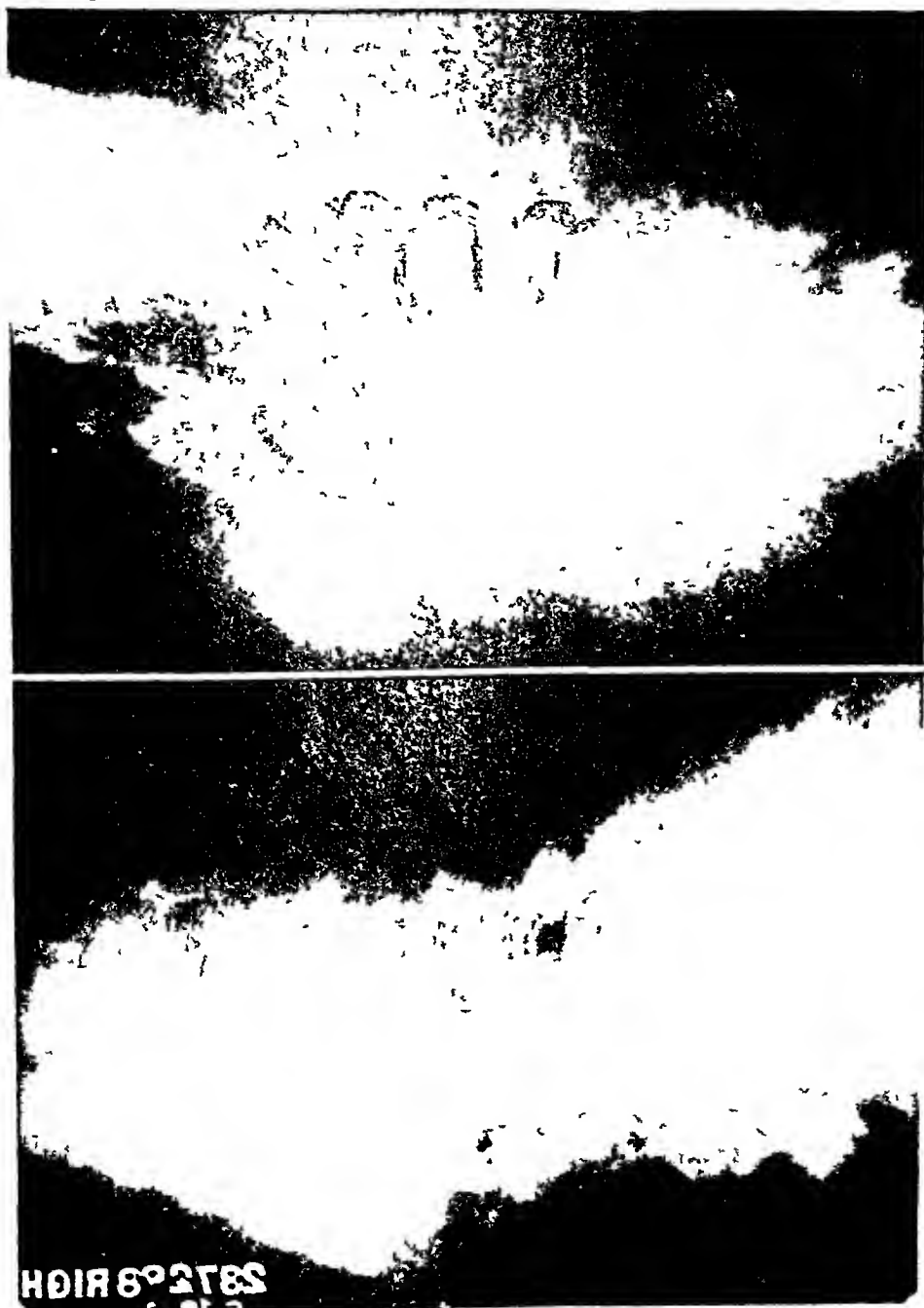


FIG. 5 Calcification in the wall of an aneurysm of the abdominal aorta anterior to the third and fourth lumbar vertebrae

FIG. 6 Erosion of the thoracic and lumbar vertebrae by an aneurysm of the aorta confirmed at autopsy. Scalloping is unusually well demonstrated

Subsequent resorption of bone results in the exertion of pressure on nerve roots and in extreme cases on the spinal cord causing paraplegia. The lowermost ribs as well as the transverse processes of the vertebrae may also be eroded.

Displacement or distortion of organs commonly occurs as the aneurysm enlarges. The diaphragm may be elevated, thereby changing the cardio-phrenic angles. The stomach may be indented, or the kidneys and ureters displaced, the latter at times being obstructed. The left ureter and kidney are affected with notable frequency. As a result of rupture followed by retroperitoneal and intraperitoneal hemorrhage, a number of distorting phenomena of the viscera may occur. By means of further extension beneath fascial planes, the subcutaneous tissues in the lumbar region and over the dorsum penis may eventually be reached<sup>16, 17</sup>. Rupture may occur into the pleural cavity, the mediastinum or the gastrointestinal tract<sup>18</sup>. Intestinal obstruction, both mechanical and paralytic, has been produced by this mechanism. Portal, splenic and mesenteric vein thrombosis have been reported<sup>2, 17</sup>. Rupture of the aneurysmal sac may result in sudden death due to a single massive hemorrhage. Terminus may be delayed if bleeding is intermittent. When this occurs the retroperitoneal connective tissue structures about the aneurysm confine the extravasated blood, and by this tamponading effect death may be delayed until the final, exsanguinating hemorrhage<sup>16</sup>. The extent of the fascial planes about the aorta has been clearly outlined by Congdon.<sup>8</sup>

*Symptoms.* Aneurysms of the abdominal aorta are notorious for the latency of their clinical expressions. Pain of a varying nature and intensity is the predominating symptom. It may be caused by hemorrhage into the perirenal space, by vertebral erosion, by pressure on the dorsal nerve roots, and by displacement of the kidney and ureter with obstruction. The pain produced by vertebral erosion and dorsal root pressure is neuralgic and is of increasing severity. It is described as boring and piercing and is usually excruciating. Infrequent cases have been reported in which pain has been absent.<sup>19</sup> It is refractory to the usual sedative measures and may be induced or relieved by alterations in intra-abdominal pressure and by postural changes.<sup>1, 20</sup> In one case reported by Uhle<sup>21</sup> exertion precipitated a paroxysm of pain which was relieved when the patient assumed the erect position. Sitting and lying prone made the pain unbearable.

The pain radiates in a characteristic fashion, frequently simulating renal colic. This has resulted in the diagnosis of primary urologic disease more often than is warranted. The report published by Uhle<sup>21</sup> presents convincing

When the vascular wall gives way and intermittent hemorrhage occurs, the pain is recurrent like that of renal colic. Since slow leakage may exist for weeks prior to the terminating episode, the two conditions may be readily confused. Nausea and vomiting are more frequent in patients who have an accumulation of retroperitoneal blood, and loss of weight and fever are common. Pain due to vertebral erosion and nerve root pressure rarely shows these characteristics.<sup>16</sup> When rupture and massive hemorrhage take place, the patient may suddenly feel something give way and may experience terrific pain soon followed by shock. Occasionally, a pulsating mass accompanied by a thrill and bruit may be found following this type of hemorrhage.

The duration of symptoms seldom exceeds one year. In the 57 cases reported by Kampmeyer,<sup>5</sup> 35 had symptoms lasting six months or less and in 51 patients symptoms had been present no more than one year.

*Physical Findings* The cardinal physical finding, when present, is an abdominal mass which is usually located in the epigastrium. It may be situated elsewhere in the abdomen, occasionally in the left subcostal region or in the loin. The mass characteristically transmits an expansile pulsation. A thrill and bruit may be noted. Kampmeyer<sup>5</sup> observed pulsations in 49 of the 50 patients who had an intra-abdominal tumor. A diminished volume of the crural pulse retarded in relation to the radial pulse has been observed. The presence of a large amount of blood clot about a perforated, intermittently bleeding aneurysm disguises the lesion because it effectually prevents the transmission of the vascular impulse, thrill and bruit. The tumor however, may be prominent.

In addition to the mass, ecchymotic areas may be present over the lumbar areas. Tenderness and muscle spasm are indications of the extent of hemorrhagic infiltration. The presence of shock is of little aid in early diagnosis. In the absence of a palpable mass, the clinical diagnosis is very difficult. The history is valuable in cases of this type because it may suggest the diagnosis or render its exclusion mandatory.

*Differential Diagnosis* The differential diagnosis involves many surgical and medical conditions, chiefly renal and extrarenal diseases. Frequent displacement of the kidney and ureter occurs because of the pressure of a dilating aneurysm and because of hemorrhage into the perinephric space. The symptoms associated with vertebral erosion and nerve root pressure may further confuse the clinical picture.

Pain produced by aneurysm of the abdominal aorta, although possessing many of the characteristics of renal pain, is rarely relieved by antispasmodics or opiates. Peritoneal irritation due to hemorrhage produces signs almost typical of an acute abdominal condition and surgical intervention may appear unavoidable. The presence of a pulsating mass is very significant and signs of progressive internal bleeding are of further aid.

From the roentgenologic point of view, hemorrhage into the perirenal space may be confused with perinephric abscess by obscuring the visualization



of the kidney and psoas shadows. Evidence of continuous blood loss, as well as the abrupt onset of symptoms associated with a mass, argues against this diagnosis. The insertion of a needle into the suspicious area may establish the diagnosis.

Intra-abdominal tumor large enough to be either palpated or visualized roentgenographically occasionally must be differentiated from aneurysm, especially if adjacent to the aorta. In this group are gastric carcinoma, pancreatic cysts, masses of retroperitoneal lymph nodes and renal tumors.

Indentation of the posterior aspect of the stomach and symptoms pointing to an intrinsic gastric lesion may be present when an aneurysm presses against the stomach. In gastric carcinoma, however, if not immobilized by extragastric extension, movement of the mass synchronous with respiration may be felt. It may be difficult to differentiate between the two lesions without the presence of vertebral erosion or the presence of an expansile pulsation in the mass. Laboratory tests may be indecisive (Case 1).

Pancreatic cysts may simulate aortic abdominal aneurysms by transmitting the vascular pulsation. Both lesions may displace the stomach anteriorly and both may contain calcific deposits. The differentiation, therefore, may at times be made only by detecting vertebral erosion or by careful study of the pulsation and recognition of its transmitted character.

Differentiation from a mass of malignant retroperitoneal lymph nodes may be difficult because not only may the mass pulsate, but vertebral erosion may occur.<sup>6</sup> The intervertebral disks, however, are destroyed in malignant diseases and the vertebrae involved present an irregular, patchy, ragged outline with a worm-eaten appearance, findings not associated with erosion due to aneurysm.

Other pathologic entities which may be simulated by abdominal aortic aneurysms include retroperitoneal sarcomata, gumma of the liver and omental tumors. The symptoms of tabetic crises, cholecystitis and cholelithiasis, lead colic, neuritis and peptic ulcer all have been closely imitated. Intestinal obstruction has been produced mechanically by this lesion and the pain has been observed to precipitate meteorismus.

*Radiographic Findings.* The diagnosis of aortic aneurysm may

in other reports, although it may be significant. The calcified aneurysmal wall following the line of least resistance presents an anterior and lateral bulge (figures 2, 3, 4, 5).

Direct roentgenographic examination of the abdomen may reveal the arteriosclerotic wall of an aneurysm as a thin curved line of calcification lateral and anterior to the vertebral column (figures 2, 3, 4, 5). Further definition may be necessary in order to establish the diagnosis. Additional contrast in the abdominal cavity may be acquired by distending the stomach with air, by producing a pneumoperitoneum or by inflating the colon.

The tumor mass is rarely of sufficient size and density to be revealed in the anteroposterior roentgenogram of the abdomen. This is particularly applicable to aneurysms located between the diaphragm and the origin of the renal arteries. Their presence may be revealed by the methods of gastric inflation and pneumoperitoneum. A filling defect of the cardiophrenic angles or obliteration of the psoas margins may occur.<sup>16</sup>

The frequency with which symptoms of an abdominal aortic aneurysm have been confused with renal disease makes the use of retrograde and excretory urography essential. Since the kidney and ureter are often displaced by an aneurysm, as has been evidenced by many postmortem examinations, the radiologist must employ urography in the investigation of abdominal aortic lesions. Five cases revealing this phenomenon of displacement have been reported within the last three years.<sup>8, 16, 17</sup> To these two additional cases are added

#### CASE REPORTS

*Case 1* C. J., a 73 year old colored janitor, was admitted because of pain in the left lower quadrant and left loin for two months. The pain was sudden in onset, sharp, intermittent and of increasing severity. He had been completely incapacitated for one month before admission. Excessive indulgence in alcoholic beverages increased the severity of his symptoms. He had lost 15 to 20 pounds during this period. There were no symptoms referable to his pulmonary, cardiovascular, gastrointestinal or genitourinary systems.

He had had syphilis 25 years before and gonorrhea on two occasions. Treatment had been received for both conditions.

At examination the patient was in no distress. He was poorly nourished. His blood pressure was 140 mm Hg systolic and 100 mm diastolic, temperature was 102° F, pulse 90, respirations 28. His sclerae were icteric. The abdomen was scaphoid and epigastric tenderness and spasticity were elicited. There was tenderness in the left lower quadrant extending from the crest of the ilium downwards and medially. Definite bilateral costo-vertebral tenderness was found. The liver edge was palpated one finger's-breadth below the costal margin.

The cerebrospinal fluid was clear. The Wassermann reaction was positive and the colloidal gold curve was pyretic.

Gastric analysis revealed a trace of blood in all specimens and achlorhydria. No lactic acid was present.

Direct roentgenographic examination of the abdomen revealed no evidence of renal disease. An intravenous urogram was normal. Examination of the stomach revealed a filling defect at the cardia interpreted as a mucopolyp.

His course was progressively downward. He became mentally sluggish, emaciated and developed urinary and fecal incontinence. He died 31 days after admission. The clinical diagnoses were cirrhosis of the liver, gastric carcinoma, lues and pyelonephritis.

Postmortem examination revealed an aneurysm of the abdominal aorta with erosion of the twelfth thoracic and first lumbar vertebrae. The thoracic aorta, especially the arch, showed longitudinal wrinkling. The abdominal aorta just above the renal arteries presented a sacculated aneurysm measuring 8 by 8 cm. In the posterior wall of the aorta at this level an oval opening leading into the aneurysm was found. The wall was thick and composed of laminated layers of brown material. Extensive vertebral erosion was present, only a thin shelf of bone remained between the aneurysm and the spinal cord. A generalized miliary tuberculosis was the immediate cause of death.

Reëxamination of the roentgenograms of the stomach taken in the oblique positions revealed scalloping of the bodies of the twelfth thoracic and first lumbar vertebrae. There was no evidence of vascular calcification (figure 1).

*Case 2.* A K, a 58 year old white man, was admitted with chills, fever up to 104° F, and cough for three weeks. Four days prior to admission his right foot had suddenly become numb and painful. There were occasional episodes of vomiting. Early in the course of his illness he complained of mild epigastric pain radiating to the left shoulder and to the left lower quadrant. There was no weight loss. His past history was not contributory.

Physical examination revealed an acutely ill, well developed and well nourished man. His blood pressure was 92 mm Hg systolic and 60 mm diastolic, his pulse was 120, and his temperature was 105° F. His left pupil was irregular and smaller than the right. His lips were herpetic and the tongue showed atrophy of the papillae. Examination of the chest revealed moist rales at both bases. The heart was slightly enlarged to percussion. There was a normal sinus rhythm and a soft apical systolic murmur. The liver was enlarged two fingers' breadth below the costal margin and was tender. There was tenderness to percussion over the right costovertebral angle. The right foot showed diminution in pain, touch, temperature and position sense. Vibratory sense was absent. The plantar reflexes were decreased. Pulsations in the right popliteal artery and its distal branches were absent.

The blood Wassermann reaction was reported as positive. Blood and stool cultures for *Salmonella cholerae* were positive as were agglutination tests for Paratyphoid A and B. The Widal test was positive. Repeated urine examinations were negative.

Roentgenographic examination of the abdomen and chest were reported as negative.

Just above the bifurcation of the abdominal aorta the vessel was dilated, forming a large globular mass. The posterior wall of the aorta was destroyed and replaced by a blood clot. There was calcification and "tree-barking" in the arterial wall.

The diagnosis of aneurysm of the abdominal aorta was not made ante mortem. Suggestions offered to explain the back pain and ileus were osteomyelitis of the sacrum and rupture of an abdominal viscus. The symptoms in the right foot were believed due to arteriosclerosis obliterans with recent insult to one of the collateral vessels and subsequent recovery. The presence of the Salmonella infection overshadowed the symptoms of the aortic lesion during the greater part of his illness. Death was caused by rupture of the aneurysm.

Reexamination of the roentgenograms of the lumbar spine in the lateral view showed the presence of a dilated abdominal aorta, fusiform in shape, extending from the level of the second to the fourth intervertebral disks with the widest diameter (5 cm) at the level of the third. Identification was made possible by the calcification in the arterial wall. No erosion was seen. The postero-anterior views were of no value in demonstrating the lesion.

*Case 3* H. R., a 78 year old man, was admitted because of pain in the right lumbar region. His present illness started four months before admission with weakness, a slight cough, and chest pain. Unusual frequency of urination and difficulty in starting the urinary stream were also present. Forty years before he had had tuberculosis.

Eight days before admission he had a sudden attack of pain in the right upper quadrant radiating to the back beneath the right shoulder blade. Three days later he was admitted to another institution where a mass was palpated in the right lumbar region. This was aspirated and a cloudy fluid loaded with pus was obtained. No bacteria or acid fast organisms were found. Urinalysis was negative.

On admission he appeared dehydrated and chronically ill. His blood pressure was 150 mm Hg systolic and 100 mm diastolic. The heart sounds were distant and frequent extrasystoles were present. The abdomen was protuberant, and no masses or viscera could be palpated. There was tenderness in his right hypochondrium and in the right lumbar region.

His course was steadily downward. Intravenous urography revealed good excretion from both kidneys. The right kidney was smaller than the left. A chest roentgenogram showed the heart to be normal. A gastrointestinal series was not contributory. No serologic reports were available.

Abdominal paracentesis yielded about 5,000 c.c. of clear fluid. No neoplastic cells were found in the sediment. Following this procedure an orange-sized movable tender mass could be felt in the epigastrium to the left of the midline.

The patient became progressively weaker, drowsy and uncoöperative. Anorexia was severe, hiccups and vomiting became frequent and abdominal distention more apparent.

The clinical diagnoses were possible right perinephric abscess, gastrointestinal malignancy, arteriosclerotic heart disease and chronic bronchitis.

At postmortem examinationiliary tuberculosis was found to be the primary cause of death. Five cm distal to the orifices of the renal arteries there was a globular distention of the aorta measuring 8 cm in diameter. The lumen was filled with a rubbery, gray-yellow mass adherent to the vessel wall but not causing occlusion. Numerous large atheromatous plaques, many of them ulcerated, were present in the ascending and descending thoracic aorta.

Reexamination of the intravenous pyelograms yielded the additional information that although the kidney shadows were normal there was a lateral displacement of the right ureter in its upper third. A thin line of calcification could be seen medially

- and parallel to the ureter just above the site of ureteral angulation at the level of the inferior margin of the third lumbar vertebra (figure 2)

The presence of this calcific deposit together with the slight displacement and angulation of the upper right ureter might well have suggested the correct diagnosis

*Case 4.* S C, a 76 year old man, suddenly had nausea, vomiting, belching and severe pains in his right loin radiating towards the midline. There was an accompanying desire to defecate but no stools were passed. The pain lasted 12 hours, after which the patient collapsed. Two years before the patient had had a similar but more brief attack.

Examination revealed an aged, poorly-nourished, feeble man. Sonorous and crepitant râles were heard at both lung bases posteriorly. The liver was palpable one finger's-breadth beneath the costal margin. An indistinct ballottable mass was palpable in the right upper quadrant. Marked right costovertebral tenderness was present. There was moderate abdominal rigidity but no rebound tenderness. His blood pressure was 106 mm Hg systolic and 50 mm diastolic. The urine was negative save for 2 plus albumin and many urate crystals. The sedimentation rate was 80 mm in one hour. The Kline reaction was negative.

A roentgenogram of the abdomen was reported as negative. Roentgenographic examination of the chest revealed an infiltrative lesion involving the lower half of the right lung consistent with the diagnosis of pneumonia.

The patient was somewhat more alert the day after admission. At this time he described his pain as originating in the right loin and radiating anteriorly across the epigastrium. Incontinence was present. His temperature rose to 101° F, and on his third hospital day he died.

The clinical diagnoses were right renal calculus, coronary occlusion and perforated viscus.

At postmortem examination there was an aneurysm of the abdominal aorta that had ruptured producing an extensive retroperitoneal hemorrhage and hemoperitoneum. There were approximately 500 cc of bloody fluid in the peritoneal cavity. The entire retroperitoneal area, particularly on the right side, was purple red in color owing to extravasated blood. Blood was also present between the leaves of the mesentery. Just above the bifurcation of the aorta and 4 cm below the renal arteries there was a fusiform dilatation of the aorta measuring 8 cm in diameter. Two cm below the origin of this dilatation there was a jagged rupture of the aorta to the right of the midline measuring 1.5 cm. The aneurysm contained a friable, laminated clot 1.5 cm thick which was attached to its wall. The arterial lumen was 2 cm in diameter. Marked arteriosclerosis was evident in the aorta. Signs of vascular atheroma both grossly and microscopically were absent.

the most prominent symptom was pain in the right lumbar area radiating to the epigastrium and around the iliac crest to the scrotum. During the week before admission his temperature had varied between 101° and 102° F.

Physical examination revealed his heart and lungs to be normal. His abdomen was distended, tense and tympanitic. Tenderness was elicited in the right upper and lower quadrants, and there was a positive right Murphy sign. His blood pressure was 145 mm Hg systolic and 90 mm diastolic.

Three days after admission edema of the right lateral abdominal wall was noted. His breath became urinous. On the fourth day there was a question whether a palpable mass was present in the right upper quadrant. Two attempts to aspirate the right kidney were unsuccessful. A mass was definitely palpated in the right lower quadrant on the seventh day. Laparotomy through a right lower quadrant incision revealed a large retroperitoneal hematoma. Soon thereafter anuria developed and persisted until death three days later.

Urinalysis on admission revealed 4 plus albumin with numerous casts. A progressive anemia developed, the hemoglobin falling from 84 per cent to 56 per cent and the red cell count from 4.2 millions to 3.3 millions. The blood serologic reaction was negative. The urea nitrogen rose from 33 to 190 mg per cent. The creatinine rose from 2.6 to 13 mg per cent.

Anteroposterior roentgenograms of the abdomen revealed linear areas of calcification 3 to 4 cm to the left of the bodies of the eleventh thoracic to the fourth lumbar vertebrae outlining a localized dilatation of the aorta with remarkable clarity. Retrograde pyelography demonstrated a lateral displacement of the right kidney and ureter opposite the first and second lumbar vertebrae, with angulation of the ureter at the level of the third lumbar vertebra. There was no ureteral obstruction (figure 3).

Wound inspection post mortem revealed a mass of clotted blood in the peritoneal cavity. A retroperitoneal hemorrhage infiltrating the posterior portion of the fat capsule of the right kidney was present. This infiltration extended from the upper pole of the right kidney to the retroperitoneal tissues in the lesser pelvis. At the level of the renal arteries there was a saccular aneurysm the size of an orange containing an organized laminated thrombus. At the lower end of the dilatation an intimal tear 2 cm in diameter was seen opposite the retroperitoneal hematoma. The renal arteries were patent, but compressed and surrounded by the thrombus. Atherosclerosis of the aorta and moderate nephrosclerosis were present.

*Case 6* S. N., a 56 year old man, was admitted because of nocturia, dysuria and pain in the lumbar region radiating anteriorly to the right groin of one week's duration.

When 15 years old the patient had a penile ulceration which was not treated. There was a history of hypertension for two years.

On admission the patient was a well developed man who did not appear to be ill. His lungs were normal. The heart was moderately enlarged to the left, and his blood pressure was 208 mm Hg systolic and 98 mm diastolic. The abdominal viscera were not palpable. A firm, non-tender mass about 7 cm in diameter was felt in the left umbilical region extending one or two cm below and to the left of the umbilicus. An expansile pulsation was noted and the mass was well circumscribed and appeared to be part of the aorta. A loud bruit was heard transmitted towards the left common iliac artery. The left femoral artery was not palpated. Pulsations of the right femoral artery were full. The blood pressure in his right lower extremity was 240 mm Hg systolic and 150 mm diastolic, in the left zero. The entire left leg was cold. Shock tenderness was present over the right costovertebral angle. The Wassermann and Kline reactions were negative.

Roentgenographic examination of the abdomen revealed both kidneys to be normal. No calculi were seen. Hypertrophic changes were present in the lumbar vertebrae. A roentgenogram of the chest was normal. Repeated studies of the lumbar spine failed to reveal erosion of the lumbar vertebrae.

The patient's symptoms subsided and he was discharged with the diagnosis of an aneurysm of the abdominal aorta. The mass did not undergo any change.

Although repeated blood and cerebrospinal fluid Wassermann reactions were negative, he was placed on potassium iodide therapy. For the next 11 months he was asymptomatic. Soon thereafter he was readmitted because of sticking pains in his left upper quadrant radiating to the lumbar region and to the right upper quadrant. The pain was sudden in onset, and was relieved by bed rest.

Examination at admission showed that the patient had lost considerable weight. The abdominal mass was described as about 8 cm long, vaguely outlined, non-tender, and located to the left of the umbilicus. The left femoral pulsation was barely palpable.

The Kline reaction was negative. Blood and urine studies were normal. The patient was discharged one week after admission.

A review of the roentgenograms made at his last admission revealed a thin calcific shadow in the wall of the abdominal aorta outlining a fusiform aneurysm. The widest diameter was at the level of the fourth lumbar vertebra. The calcification could be seen only in the lateral projection.

*Case 7* H. K., a 64 year old man, was admitted because of back pain for 10 days. For the past nine years he had had anginal attacks. Two years previously he had been bedridden for six months following a coronary occlusion. There was also a past history of ankle edema and intermittent claudication for eight years while orthopnea and a chronic cough had been present for two years.

During the 10 days before admission he had a dull, severe, almost continuous non-radiating pain in the left lumbar region which increased in severity after eating. Relief could be had by drinking milk during the early part of his illness. He later observed that the pain was alleviated by assuming the recumbent position.

Examination revealed a poorly-developed white man who appeared to be comfortable. His heart and lungs were not remarkable. The abdomen and breasts were large, pendulous and of a feminine type. No organ edges or masses were noted. Lumbar tenderness was marked and very slight left flank tenderness was elicited. There was a marked dorsal kyphosis. Pubic hair was almost absent and his testes were small.

The diagnosis on admission was a polyglandular syndrome of the hypogonadal type. A neoplasm or cyst of the pancreas was considered.

Roentgenograms of the lumbar spine revealed moderate hypertrophic osteoarthritis. In the lateral projection it was possible to demonstrate calcification in the abdominal aorta outlining a fusiform dilatation extending from the second lumbar intervertebral space to the center of the body of the fourth lumbar vertebra. The greatest diameter, 4 cm, was seen at the level of the body of the third lumbar vertebra. Both the anterior and posterior walls of the calcified vessel were seen in the lateral projection. The dilatation was principally anterior, the posterior wall being straight. There was no bone erosion (figure 4).

The diagnosis of a calcified aneurysm of the abdominal aorta was considered established. The roentgenographic findings were the only means of identifying the lesion accurately inasmuch as neither the history nor clinical findings at the time suggested its presence.

*Case 8* D. P., a 67 year old white man, was admitted because of recurrent pains in the lumbar region radiating down the right thigh for nine weeks. The onset of these attacks was sudden, and the pain was described as sharp. The attacks lasted

from one to one and one-half hours, and recurred at intervals of from one to three days. The last episode occurred the day of admission after a remission of about four days.

Six years ago he had had a coronary thrombus following which his activity was restricted. Symptoms of prostatism had been present for two years. No history of syphilis was elicited.

On physical examination his heart was not enlarged. A short, soft systolic murmur was heard over the mitral area. His blood pressure was 170 mm Hg systolic and 110 mm diastolic. The abdomen was soft. A large, firm, smooth, non-tender, elliptical mass was palpated in the right lower quadrant. It was deeply fixed and transmitted an expansile impulse synchronous with the heart beat and appeared to be continuous with the aorta. No lumbosacral or sacroiliac tenderness was present. There was moderate atrophy of the right lower extremity, most evident in the thigh. Rectal examination revealed a symmetrically enlarged, soft, tender prostate. Neurologic examination was negative except for motor weakness of the left lower extremity and a positive Lasgue's sign on the right side. The blood and cerebrospinal fluid serology were negative.

Roentgenographic examination of the lumbar spine and pelvis revealed advanced osteoarthritic changes affecting the first and second lumbar vertebrae. Intravenous urography showed both kidneys to function normally. The lower portion of the right ureter was not visualized, the upper portion was normal.

An air contrast enema study of the colon failed to reveal any local pathologic lesion. There was, however, a slight increase in density over the right wing of the sacrum. Whether this was due to the pulsating mass noted on physical examination could not be stated with certainty. It was noteworthy that a roentgen-kymogram taken after the rectal instillation of air showed pulsations in this region synchronous with the heartbeat.

Laminagraphic studies of the abdomen were not helpful. A pneumoperitoneal study was reported as follows: "in the right abdomen above and overlying the inner margin of the ilium, as well as the adjacent portion of the sacrum, there is a semi-opaque mass which on oblique study apparently projects slightly forward. Though one cannot state exactly its true nature, I am inclined to believe from its tapering appearance and the fact that it pulsates that we are dealing with an abdominal aneurysm of the lower aorta."

The discharge diagnosis based on clinical and roentgenologic evidence was an aneurysm involving the abdominal aorta and right iliac artery.

*Case 9.* Z. L., a 74 year old white woman, was first seen at the Hospital in 1939 for an acute hemorrhagic cystitis. She also had hypertension and a large umbilical hernia. Subsequent admissions in 1941 and 1942 for recurrence of the cystitis and pyelonephritis were recorded. In the course of radiographic examination of the lumbar spine a markedly calcified abdominal aorta was found with a definite anterior bulge indicative of aneurysmal dilatation. No masses or palpable viscera were noted. The Kline reaction was negative.

The roentgenograms revealed the aneurysm to be fusiform in shape, extending from the second to the fourth lumbar intervertebral spaces, the widest diameter being at the level of the third. The anteroposterior roentgenograms were of no aid in defining the lesion. The vertebral bodies were intact (figure 5).

In this case the aneurysm was found in the course of routine roentgenographic examination.

## DISCUSSION

The correct diagnosis was made in four of the nine cases reported here. There were eight men and one woman in the series. The symptoms pro-



duced by the lesion were mostly those suggestive of renal disease, resulting in the diagnosis of renal calculus, pyelonephritis and perinephric abscess. Gastrointestinal malignancy was considered in two cases, an appendiceal abscess in one, and a perforated viscus in another. The presence of two patients dying of miliary tuberculosis in a small series is of interest.

Seven of the patients complained of back pain, and in three it radiated to the groin and the lower extremity. The pain was either intermittent or persistent in character and was relieved by postural changes in two patients. The severity varied from mild in the less extensive cases to a shocking intensity in patients in whom rupture occurred. Ileus following perforation occurred in two patients. The duration of symptoms in five patients examined post mortem was two years in one and varied from 24 days to four and three-quarter months in four others. This is in accord with Kampmeier's findings.<sup>5</sup>

In two patients the diagnosis of calcified aortic abdominal aneurysm was made as an incidental observation. These individuals had few or no symptoms or physical findings to direct attention to the presence of the aneurysm, and the roentgenograms alone established the diagnosis.

The physical findings of importance were few, but when present were significant. An intra-abdominal mass was palpated in three patients, and in two of these an expansile pulsation was felt. Tenderness and muscle spasm were frequently encountered in the lumbar area and in the anterior abdominal wall in either the upper or lower quadrants or both. In one patient, the tenderness over the lumbosacral spine suggested osteomyelitis. In another patient the presence of an aneurysm was unrelated to her illness. The right side was affected as regarded both symptoms and physical findings in five cases, the left in three. The predominance of right-sided symptoms and signs was unusual because the cases reviewed from the literature indicated that the left side was more frequently involved.

Roentgenographic examination was the most fruitful of the laboratory procedures. Of the four cases in which the correct diagnosis had been established all were alive at the time of writing. In each the roentgenogram either made the diagnosis or confirmed the clinical impression. Of the five patients who died and were examined post mortem the diagnosis had not been made before death although roentgenologic examinations were available. A review of these roentgenograms revealed sufficient evidence to suggest the possibility of an abdominal aortic aneurysm in each.

Calcification in the dilated vascular wall was present in six patients and was the most frequent finding. The ages of the patients in this group varied from 56 to 76 years. Angulation of the ureter was present in two cases, and the kidney was displaced and rotated in one. A semi-opaque pulsating mass could be outlined roentgenologically in the eighth patient after artificial pneumoperitoneum was induced. A filling defect in the cardia of the stomach was observed on the films taken during a gastrointestinal examina-

tion of one patient. Vertebral erosion was subsequently noted on these films.

The serologic reaction was positive in two cases. In both, autopsy revealed the presence of vascular syphilis. A serologic reaction was not available in one patient who had no evidence of syphilis post mortem. Other laboratory procedures were of little help.

### SUMMARY

This review and the cases of aortic abdominal aneurysm presented here may focus attention on the importance of painstaking roentgenological examination in the diagnosis of this obscure malady. The most recent contribution has been made by intravenous urography. The importance of identification of vascular calcification must be stressed, because even a thin, small deposit may, by its location, lead to a proper diagnosis. Pneumoperitoneum was helpful in one case.

The importance of a carefully taken clinical history and a thorough physical examination is apparent. They furnish the fundamental criteria upon which the diagnosis is established, and indicate the proper roentgenologic procedures necessary to facilitate investigation.

I would like to thank Dr. B. S. Epstein and Dr. E. L. Shlevin for their help and encouragement.

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# CASE REPORTS

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## PRIMARY SPLENIC NEUTROPENIA, WITH REPORT OF A CASE\*

By MOSES SALZER, M D, J LOUIS RANSOHOFF, M D, and HERMANN  
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ABOUT one year ago Wiseman and Doan<sup>1</sup> published a report of five cases of "a hitherto unrecognized cause of neutropenia resulting from a pathologically altered, physiologic function of the normal spleen" They labelled this disease "primary splenic neutropenia" They postulated the theory that the spleen has a selective destructive action on the various cellular components of the blood For instance, in thrombocytopenia, this selective destructive function destroyed the thrombocytes at an abnormally high rate, in hemolytic jaundice the erythrocytes were selected for destruction, whereas in "primary splenic neutropenia" the neutrophils were the victim of this selective action In no instance was there any interference with hematopoiesis as was evidenced by a normal bone marrow Proceeding on this theory splenectomy was performed on these patients with a complete and permanent cure of their disease

The case we are about to report fulfilled the criteria set up by them, probably in a purer form, because, owing to their publication, it was recognized earlier, and the spleen was removed rather early in the course of the disease on the advice of Dr Charles A Doan, who studied the slides of the blood and the bone marrow Our case showed no secondary anemia of any consequence, no diminution in the platelets and no jaundice, which was evident in whole or in part in their cases, which had had a more prolonged illness

### CASE REPORT

Mrs G G, aged 59, housewife, was admitted to the Jewish Hospital on November 9, 1942 She had been seen by one of us at her home four days before her admission to the hospital At that time she complained of chills alternating with fever Her temperature was slightly elevated, but the physical examination was essentially negative She did not appear very ill and aspirin was prescribed for her There being no improvement in her condition during the succeeding four days, she decided to enter the hospital

Her past history revealed that 11 months before, she had been confined in another hospital, with a diagnosis of pneumonia Her blood count at that time showed erythrocytes 4,970,000 per cu mm, leukocytes 2,750, with 24 per cent polymorphonuclear neutrophils She was confined to her bed almost continuously for the next five months, but gradually was able to assume some, but not all of her household duties at the time of the onset of her present illness

On admission her temperature was 101.6° F, pulse 124, and respirations 30 per minute There was no cough and there were no other symptoms, excepting the

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chills and fever The physical examination revealed the spleen to be slightly enlarged, being barely palpable on deep inspiration

No superficial lymph glands could be felt There were no other physical findings of importance at this time Her blood count showed erythrocytes 4,700,000 per cu mm, leukocytes 2,000, polymorphonuclear neutrophils 50 per cent, lymphocytes 40 per cent, monocytes 10 per cent, hemoglobin 10.5 grams This count was rechecked in two hours, and the leukocyte count had dropped to 1350 On the next day, November 10, 1942, the leukocyte count was repeated It was then 1300, with essentially the same differential count as the day before The reticulocytes numbered 17 per cent and the platelets 204,000 On this day she was given a transfusion of 250 cc of whole blood Her symptoms and physical examination remained unchanged Her maximum temperature was 101.6° F on that day The next day, November 11, she appeared to be more acutely ill, and that afternoon her temperature rose to 105.2° F Her respirations were 40 per minute and her pulse 132 The physical examination showed some evidence of consolidation at the base of the right lung, which was confirmed by roentgen-ray film The spleen was definitely enlarged and easily palpated

Her blood count at this time showed erythrocytes 4,500,000 per cu mm, and leukocytes 800 with polymorphonuclear neutrophils forming only 36 per cent of the total

A sternal puncture was done by Dr Harold K Moss and the aspirated marrow was submitted to Dr Philip Wasserman, Laboratory Chief of the Jewish Hospital, and to Dr Charles A Doan of the Ohio State University, and both pronounced it essentially normal There was apparently no defect in the blood forming mechanism Despite the low leukocyte count she was given 5 grams of sulfadiazine intravenously, as it was felt that the pneumonia was responsible for the change in her condition An additional 4 grams was given by mouth during the next 36 hours There was a prompt drop in her temperature and a marked improvement in her general condition The spleen diminished in size and was no longer palpable after a few days

On November 12, 1942 her blood count showed erythrocytes 4,810,000 and leukocytes 1,500 per cu mm of which 45 per cent were neutrophils On the next day the erythrocytes numbered 5,120,000 per cu mm, and the leukocytes 950 of which 32 per cent were neutrophils

Following this she was given no medication of any kind Her general condition improved, as did her appetite She stated that she felt better each succeeding day During the next two weeks, however, her leukocyte count did not exceed 1,950 per cu mm It was as low as 750 per cu mm and several days in succession it did not exceed 800 During this time the neutrophils reached an all time low of 9 per cent

Suddenly, on November 25, 1942 she experienced a severe stabbing pain in the lower left chest, accompanied by a chill and a rise in temperature to 102° F A distinct friction rub could be elicited and a roentgen-ray film confirmed the clinical diagnosis of pleurisy This film also showed that the pneumonia in the right lower lobe had completely healed With the onset of the pleurisy the spleen again became easily palpable Her blood count at this time revealed erythrocytes 4,130,000 per cu mm, and leukocytes 1,450, of which 30 per cent were neutrophils Coincident with her improvement from this attack of pleurisy her leukocyte count again dropped so that on November 29, 1942 it was 700 with the polymorphonuclears forming 32 per cent of the total The spleen was no longer palpable

Numerous platelet counts showed them always to be in excess of 200,000 per cu mm

We felt that a splenectomy was imperative and this was performed on December 12, 1942 Just before operation her blood count was as follows. Erythrocytes 3,790,-

000 per cu mm, leukocytes 1,400, polymorphonuclears 22 per cent, lymphocytes 51 per cent, and monocytes 17 per cent

The artery was clamped at 10 55 a m, and a count taken immediately showed 7,550 leukocytes per cu mm. At 1 p m there were 6,000 leukocytes per cu mm with 82 per cent polymorphonuclears. Two days later the leukocyte count had risen to 14,650 per cu mm with 87 per cent polymorphonuclears. Her recovery was uneventful and she was discharged from the hospital January 1, 1943. On the day of her discharge her count showed erythrocytes 3,710,000 per cu mm, leukocytes 3,950, polymorphonuclears 59 per cent, platelets 486,010.

A count made on January 16, 1943 was as follows: Erythrocytes 4,630,000 per cu mm, leukocytes 4,300, hemoglobin 10.9 grams, polymorphonuclears 55 per cent, lymphocytes 29 per cent, mononuclears 11 per cent, eosinophiles 3 per cent, basophiles 2 per cent.

The patient was seen last on April 3, 1943. She was feeling perfectly well, and was able to attend to most of her household duties. Her count on that day was as follows: Erythrocytes 6,320,000 per cu mm, hemoglobin 10.8 gm, leukocytes 12,450, of which 76 per cent were neutrophils. Her general condition was steadily improving.

The description of the spleen by Dr. Philip Wasserman is as follows:

*Gross Description.* Specimen consisted of a spleen that weighed 570 grams. The spleen measured approximately 15 by 11 by 9 cm in diameter. The capsule was tense and purplish in color. On section tissue was coherent and purplish red in color. Malpighian bodies and trabeculae were poorly made out. There were no areas of infarction, defect formation or neoplasm.

*Gross Diagnosis.* Splenomegaly (570 grams).

*Microscopic Report.* Spleen. Three sections. All showed essentially the same picture. Malpighian bodies were about average in size but were more widely spaced than average. No appreciable abnormality was seen here. The central arterioles showed somewhat thickened walls and apparent slight hyaline change present. The pulp showed a picture of fibrosis with apparently overly prominent reticulum. Sinusoids in places were distinctly dilated and in many areas the lining cells of the sinusoids were bulbous, swollen and present in several layers. In many areas the detail of the sinusoids was not well made out. There was a rare large cell present in the sinusoid or attached to the wall that appeared to be phagocytic and that apparently enclosed a recognizable polymorphonuclear leukocyte or a red blood cell. No areas of hemorrhage or of infarction were seen.

*Final Diagnosis.* Splenomegaly with apparent fibrosis and reticulum proliferation (spleen of a case of splenic neutropenia).

Before splenectomy the case we have presented showed a tendency to repeated infections, owing doubtless to the low white count, but particularly to the low polymorphonuclear count. Of interest also, was her response to sulfadiazine during her attack of pneumonia, although her total white count at that time was only 890 per cu mm. Her prompt and complete recovery following the splenectomy was in striking contrast to the very slow convalescence and incomplete restoration of health following the attack of pneumonia 11 months before. When this paper was written the patient was in perfect health.

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## SUBACUTE BACTERIAL ENDOCARDITIS; REPORT OF A CASE WITH APPARENT FAILURE OF SULFONAMIDE PROPHYLAXIS COMPLICATED BY MASSIVE HEMOPERITONEUM \*

By DAVID H CLEMENT, Captain, M C, A U S, and WARREN R MONTGOMERY, Captain, M C, A U S

THE bizarre and protean manifestations of subacute bacterial endocarditis have been well described by numerous competent observers in recent years<sup>1, 2, 3</sup>. Although the treatment of this condition at present remains very unsatisfactory, we have of late acquired a better understanding of its pathogenesis. For over three decades the importance of the *Streptococcus viridans* in the etiology of this syndrome has been known. It has also been realized that this organism is most commonly found in the upper air passages and about the teeth and gums. The causal relationship of the extraction of teeth to this disease, especially in the presence of caries and pyorrhea, has been stressed by a number of writers, not only in the field of internal medicine but also by bacteriologists and dentists. Indeed, it is perhaps unfortunate that a greater number of internists are not more conversant with the numerous excellent papers on this subject which have appeared in the dental literature.

In the case of a patient with valvular or congenital heart disease suffering from pyorrhea or dental caries, or both, the physician is faced with an extremely difficult decision. He finds himself between the Scylla of leaving the focus alone and permitting it to grow worse and further menace the health of the patient on the one hand, and the Charybdis of extracting the infected teeth with the resulting hazard of having bacteria thus dislodged into the bloodstream settle on the deformed structures of the heart on the other. This dilemma is only intensified if the patient is suffering from active rheumatic fever which has shown no tendency to subside over several months. Under such conditions it would seem possible that the streptococcal focus in the teeth might even be etiologically significant in continuing the rheumatic activity. At least it would be reasonable to hope that if the focus could be removed without complications the patient would be in a better position than before.

For some years, many writers in medical and dental journals have stressed the fact that the extraction of carious teeth frequently is the precipitating event in the pathogenesis of subacute bacterial endocarditis. Only relatively recently, however, has another aspect of the problem been emphasized, namely, that individuals suffering from dental caries with or without pyorrhea are prone to have transient bacteremias spontaneously, whether or not their teeth are treated. In fact it is probable that a number of cases of subacute bacterial endocarditis which have been recognized shortly after tooth extraction were in fact already established at the time of the extraction because of preoperative spontaneous bacteremias.

The classic work of the English bacteriologists Okell and Elliott<sup>4</sup> is now well known. These investigators took blood cultures both before and after tooth

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From the Medical Services of the Children's Hospital of Buffalo, New York and of the Josephine Goodyear Convalescent Home, Williamsville, New York.

extraction in 138 patients. The incidence of positive cultures after the extractions was found to vary from 34 to 75 per cent, roughly paralleling the severity of the caries and pyorrhea and the number of teeth removed. It is very significant, however, that in 110 of these patients who had appreciable pyorrheal disease, 12 or 10.9 per cent were found to have had positive blood cultures at the time of the examination, before any surgical procedures were undertaken. Surely no more convincing proof is needed to show that patients with infected mouths do suffer at least transient spontaneous bacteremias. In patients with cardiac deformities, the hazards from the standpoint of bacterial endocarditis are perfectly obvious. Merely to leave such mouths alone is to subject the patient to repeated insults which may well lead to disaster. Feldman and Trace<sup>5</sup> several years ago, in discussing the problem of bacterial endocarditis following the removal of teeth or tonsils, described a patient of theirs who had refused to have his infected teeth extracted. Three weeks later, however, with his teeth still untouched, the patient developed low-grade fever, abdominal pain, melena, splenomegaly, positive blood cultures and the classical picture of subacute bacterial endocarditis. They conclude "Had his teeth been removed, we would have ascribed the endocarditis in this case to the operative procedure. Is it not conceivable that the infection may already be present in some cases when foci of infection are removed?" Libman, in writing on this subject, has expressed the same view.

With the advent of sulfonamide chemotherapy, it was naturally hoped that the situation in subacute bacterial endocarditis might be ameliorated, both from the standpoint of therapy and prophylaxis. As for the former, we have met with great disappointment. From the end of prevention, however, the outlook is brighter. Early in the development of sulfonamide therapy, it was shown<sup>6</sup> that *Streptococcus viridans* is generally inhibited in its growth when cultured in beef infusion broth containing sulfanilamide in a concentration of 10 mg per cent. It soon became evident that in patients suffering from subacute bacterial endocarditis with persistent *Streptococcus viridans* bacteremia it was possible to sterilize the blood stream for varying periods of time by the administration of sulfanilamide, although the essential course of the disease generally was unaltered.<sup>7</sup> That some strains of *Streptococcus viridans* were more susceptible than others to sulfonamide therapy has been stressed by various investigators.<sup>8,9</sup> Such observations naturally make the use of these drugs seem very reasonable from the prophylactic standpoint, even though in fact from a therapeutic angle they remain unsatisfactory in destroying bacteria once they are buried in a vegetation.

In 1940, Hageman<sup>9</sup> suggested the prophylactic use of sulfanilamide in patients with valvular heart disease who were to have dental extractions. He laid down no definite plan of attack. In 1941 Clagett and Smith<sup>10</sup> reported a definite routine for such patients, recommending hospitalization whenever possible, giving the drug (sulfapyridine then) until a blood level of 6 mg per cent had been obtained, extracting offending teeth, and stopping the drug only after the socket was adequately healed. This regimen they recommended for patients with a history of heart disease or physical signs of heart disease (type not specified). The ultimate proper evaluation of such a program will take time. Its logic cannot be denied.



Looking at this disease from another direction, we have been much impressed by the variety of mechanisms which work to destroy the patient. General toxemia and anemia are almost invariably present. Embolic phenomena occur sooner or later in most cases, and their failure to suppurate has been commented upon by many observers. But the importance of the mycotic aneurysm in this disease is the feature we should like to discuss briefly. Although there is some debate as to the mechanism by which such aneurysms are formed, there is no longer any doubt that they are not rare in subacute bacterial endocarditis and that their rupture may be very significant clinically. The arterial wall is perhaps infected most often by bacteria in the blood stream lodging in it by way of the vasa vasorum, though infection through the intima is another possibility. In many instances, these mycotic aneurysms first make themselves known at autopsy.<sup>1</sup> On the other hand, rupture of mycotic aneurysms in this disease may be the cause of sudden death. When this occurs, the disaster results more often from the location of the hemorrhage than its amount. In other words the patient is more seriously threatened from the fact that the hemorrhage takes place in a vital area (e.g., brain) than from exsanguination.

In reviewing the literature, we have not found a case reported in which massive hemoperitoneum occurred. Because we recently had under our care a patient who suffered from such a condition, because it was puzzling to us at the time and yet was fortunately treated successfully, we report our experience in the hope that it will perhaps help others in the diagnosis and management of these very difficult patients. At the time our patient developed this complication we were confronted with the combination of active rheumatic fever with rheumatic heart disease, severe epigastric pain, hepatomegaly and splenomegaly, marked anemia which failed to respond adequately to repeated transfusions in quick succession, increasing abdominal distention with ileus and signs of peritoneal irritation, absence of blood in the stools, and the presence of marked leukocytosis. Medical, surgical and cardiac consultants could not make the diagnosis or agree on the advisability of surgical intervention. Indeed even after laparotomy, the true nature of the lesion was not fully appreciated.

In addition to the foregoing unusual and challenging episode (from which the patient recovered only to die one month later of a cerebral hemorrhage), we record our experience because it is an example of an apparent failure of sulfadiazine therapy before, during and after tooth extraction to prevent the development of subacute bacterial endocarditis in a patient with rheumatic heart disease.

#### CASE REPORT

This child (D. B., born February 19, 1931, died May 31, 1942, Children's Hospital File Number 35866) was seen in the Out-Patient Department of The Children's Hospital at least yearly from the age of two years and five months until the time of his death at age 11 years and three months. Generally he made several clinic visits each year so that a fairly complete record of his progress is available.

At the time of his first visit (age 2 years 5 months), it was learned that his birth and family histories were not remarkable. The past history revealed that he had suffered from frequent attacks of tonsillitis, otitis media, and cervical adenitis. Because of this history and the presence of large, chronically infected tonsils, the Ear, Nose and Throat Service recommended that his tonsils and adenoids be removed and

this was done shortly thereafter. During the next two years the child showed a normal weight gain and was well with the exception of mild upper respiratory infections. In March 1935, when four years old, the child was seen for a routine examination at which time a history of migratory joint pains for one month with fever was elicited. When seen he was symptom-free. The only positive physical findings were mild cervical adenopathy and a systolic murmur which was maximal over the pulmonic area. Thereafter he did well, showing normal weight gain, and frequent examinations of the heart clinically and roentgenographically revealed no significant abnormalities.

Because a heart murmur was noticed when the patient was hospitalized for excision of a fibroma of the right thigh in June 1941 (age 10 years), he was seen by the Cardiac Service. Their findings included apparent enlargement of the heart to the left (not confirmed by roentgenogram), and a loud, 3-4 plus, high-pitched diastolic murmur of aortic quality over the entire precordium, heard best at the aortic area. Blood pressure was 115 mm Hg systolic, with no diastolic reading obtainable. The electrocardiogram was within normal limits. Their diagnosis was aortic insufficiency, Class I. It is noteworthy that the child had maintained a normal weight curve up to this time, but thereafter showed a gradual downward trend as long as he lived. During the next six months repeated examinations revealed no new findings. In December 1941, the corrected erythrocyte sedimentation rate (Wintrobe) was normal, although the hematocrit was 37 per cent and the hemoglobin 13.2 grams.

In January 1942 (age 10 years 11 months) this boy was admitted to the hospital with active rheumatic fever characterized by general malaise, pallor, fever, right ankle pain of one week's duration, and a corrected sedimentation rate of 12 millimeters at one hour. Within one week he was symptom-free and was discharged to the hospital's convalescent home where he was seen weekly by one of us.

On February 4, 1942, shortly after admission to the Convalescent Home, the patient complained of toothache. Signs of a periapical abscess of the first deciduous upper left molar were found. Root canal drainage was instituted February 5, 1942. Extraction at this time was deemed inadvisable because of the acute nature of the infection. Although the inflammatory process gradually subsided, the child continued to run a low-grade fever for the next two and one half weeks. At the end of this time he appeared to have received maximum benefit from the drainage. Since the fever persisted, however, it was felt that the remaining focus represented a serious menace to his rheumatic state. In order to break a vicious cycle, extraction of the tooth was thought justifiable, provided that it was done only after the patient had been adequately saturated with sulfonamide.

With this in mind, the patient was readmitted to the hospital for tooth extraction. On February 25, 1942 the diseased tooth was extracted as well as the adjacent molar which also appeared to be involved in the infectious process. For three days before and three days after dental surgery he received four grains of sulfadiazine daily. Although sulfadiazine blood levels were not obtained on this admission, it is to be noted that on the day surgery was performed, crystals of the drug were present in the urine in abundance. Furthermore the patient received the conventional full dosage of one grain per pound of body weight every 24 hours.

During this admission he ran a low-grade fever, reaching 101° F rectally almost daily. The pulse rate averaged 100. Repeated examinations of the heart during his stay revealed no changes from those already noted. A blood culture (with para-aminobenzoic acid) taken five days after the oral surgery, was sterile. Also at this time, the corrected sedimentation rate (Wintrobe) was 10 millimeters at one hour, the hematocrit was 27 per cent and the hemoglobin was 12 grams. The patient was returned to the Convalescent Home on March 6, 1942.

Here the boy appeared essentially unchanged for about 10 days. On March 15

1942, 18 days after tooth extraction, he had a sudden rise in temperature to 103° F by mouth and several small erythematous lesions appeared on his arms and legs. There were no subjective complaints. During the following week his temperature gradually returned to normal where it remained for 10 days.

Early in April the patient complained of pains in his hands, hips, and feet. Fever returned. On April 9, 1942, five weeks after tooth extraction the spleen was felt 3 centimeters below the costal margin for the first time. No evidences of embolic phenomena were discernible at this time. Examination of the heart, however, revealed apical systolic and diastolic murmurs which had not previously been present. On April 23, 1942 the patient began to complain of epigastric discomfort. The only new finding on physical examination was the fact that the liver edge was 3 centimeters below the costal margin. During the next four days, the child, although essentially afebrile, showed a rising pulse rate. The epigastric pain grew progressively more severe. On April 27, 1942 he complained of very severe abdominal pain and fainted for a brief interval. He was again readmitted to The Children's Hospital.

Admission examination disclosed an acutely ill, pale child complaining of marked abdominal pain. The temperature was 98° F, pulse 130, respirations 20 and blood pressure 130 mm Hg systolic, no diastolic reading obtainable. The skin was clear. The mouth appeared to be in good condition, though there was marked pallor of the mucous membranes. The lungs were not remarkable. The cardiac findings were essentially as previously described, i.e., double mitral and aortic murmurs. The abdomen was strikingly distended and peristalsis could not be heard. There was tenderness in both upper quadrants, more on the left, with definite rebound tenderness throughout the entire abdomen. The upper abdominal pain was aggravated by deep inspiration. No fluid wave was demonstrable, and liver and spleen were not felt, though distention and tenderness made examination unsatisfactory. Rectal examination revealed some fullness and tenderness anteriorly but no definite masses were made out. The stool was normal in appearance. Reflexes were physiological at this time. Laboratory findings revealed a profound anemia. Hemoglobin 7.5 grams, red blood cells 2,900,000 with a hematocrit of 21 per cent. A marked leukocytosis of 48,300 was accompanied by a differential white cell count showing a moderate shift to the left. Urinalysis was normal. The blood non-protein nitrogen was 36.4 mg per cent. Roentgenographic examination of the chest revealed clear lung fields and a cardiac silhouette showing some preponderance of the left ventricle but with no actual enlargement of the heart.

During the next three days the patient remained in a precarious condition. Because of clinical and laboratory evidences of blood loss, he received three transfusions totaling 950 cc of whole blood during this time. In spite of transient rises following transfusions, the red count and hemoglobin remained at critical levels, and the hematocrit fell steadily to 16 per cent. On the third day there was still a significant leukocytosis of 33,400. Daily measurements of the abdominal circumference revealed progressive enlargement. Audible peristalsis remained absent and on the third day a fluid wave and shifting dullness could be demonstrated. Repeated examinations of the stool for occult blood were negative.

On the second day a surgical consultant, admitting an intra-abdominal vascular accident most probable, felt that since there was no blood in the stools, there had been no interference with the intestinal blood supply and he favored a diagnosis of splenic infarction with hemorrhage. In view of the patient's condition, he recommended conservative therapy. On the same day the patient was seen by a cardiac consultant whose opinion was that a hemorrhage into the peritoneal cavity had occurred and that laparotomy should be performed within 24 hours if the condition of the patient failed to improve. Because in the following two days the child grew gradually worse, evidence of blood loss continued, and abdominal distention and ileus persisted, all consultants agreed that laparotomy was the only recourse.

Operation was performed on April 30, 1942. Under nitrous oxide, oxygen, and ether anesthesia, and with a transfusion of whole blood running, the abdomen was opened through a left rectus incision in the upper third of the abdomen. The peritoneum was under tension. The peritoneal cavity was found to be completely filled with clotted blood which was removed. Examination of the small bowel disclosed a dusky loop about 15 cm long in the upper portion of the jejunum. The impairment of circulation here seemed to be due to a thrombotic process which had started about 5 cm distal to the root of the mesentery in this area. Hemorrhage had taken place between the two layers of the mesentery beyond this point, distending them with a large clot about 8 cm square and 2 to 3 cm in thickness. One layer of the mesentery had previously ruptured, and through the opening blood could be seen oozing into the peritoneal cavity.

Several small radial incisions were made in the mesentery and through these the entire clot was evacuated. Approximately six bleeding points were then evident in the mesentery and sutures were placed for their control. Following the removal of the clot and ligation of the bleeding points, the bowel was seen to assume better color and no great impairment in its circulation could be observed. Further examination of the mesenteric vessels was omitted because of the patient's precarious condition, and the abdomen was closed without drainage. It is noteworthy that the true etiology of the hemorrhage was not established at the time of operation.

Postoperatively the patient's condition showed dramatic improvement. Response to transfusion was prompt and now brought significant rises in hemoglobin and hematocrit levels. The child continued to run a low-grade fever throughout his remaining month of life, with average daily rises to 101° F. There were no evident surgical sequelae. The wound healed normally. The abdomen resumed its normal contours, the appetite improved, and the bowels moved regularly. On the thirteenth postoperative day, the boy complained of pain in his left upper quadrant and the spleen was found enlarged and tender. Although previous blood cultures had been sterile, a culture taken on the fourteenth day postoperatively yielded *Streptococcus viridans*, 4 colonies per cc (Paraminobenzoic acid was added to the culture media). Upon identification of this organism, sulfadiazine by mouth was started in dosage of 1 grain per pound body weight every 24 hours and so maintained until death. Nevertheless *Streptococcus viridans* was repeatedly isolated from subsequent cultures. A small petechial hemorrhage appeared on the tip of the nose on the twenty-eighth postoperative day.

On May 31, 1942, just one month after operation, the child suddenly developed a severe right frontal headache and flexion of the neck became painful. Three hours later projectile vomiting occurred and there were neurological signs of increasing intracranial pressure. Bizarre and profound reflex changes appeared terminally. Seven hours after the onset of his frontal headache he lapsed into coma. Blood pressure rose, respirations became irregular and he died three hours later.

Postmortem examination was performed 11 hours after death by Dr. Koriel Terplan. An abstract of the autopsy protocol follows. Both lungs showed fairly recent passive hyperemia and slight hemosiderosis. There were scattered petechial hemorrhages in the visceral pleura and in the mucosa of the trachea and bronchi. The pericardial sac contained 15 cc. of serous fluid (normal). The heart was considerably enlarged. It weighed 250 grams (normal 122 grams).<sup>21</sup> The left ventricle was hypertrophied and dilated. The wall of the left ventricle measured 1.7 cm in thickness (normal 1.0-1.2 cm), that of the right measured 0.3 cm (normal). The circumference of the mitral valve was slightly increased and attached to its anterior leaflet was a soft friable vegetation about 3 by 4 by 2 mm. A few similar but minute, grayish-white vegetations were seen around the upper parts of the chordae tendineae of the anterior papillary muscle. The aortic leaflets were distinctly reduced in height and at the inner aspect of the right leaflet there was a coarse granular veg-

tation The line of closure was definitely thickened There were also a few friable vegetations attached to the left leaflet The aorta was normal, as were the coronary arteries In the posterior wall of the left ventricle there was a nodular scar about 3 cm in diameter Scarring was also noted in the apices of the papillary muscles

The abdominal cavity contained no free fluid The site of previous hemorrhage in the mesentery was completely healed There was distinct hemosiderotic discoloration of the peritoneum in this area Several sutures remained around a third-order branch of the superior mesenteric artery, about 3 cm proximal to the intestine Just distal to these ligatures could be seen the remains of an old ruptured mycotic aneurysm In a second-order branch of the superior mesenteric artery, was found a second, cherry-sized, mycotic aneurysm with definite hemorrhages in its wall The entire intestinal tract was otherwise normal in appearance

The spleen was greatly enlarged, weighing 400 grams (normal 87 grams) There was a huge mycotic aneurysm of the splenic artery at the hilus of the spleen This measured  $2\frac{1}{2}$  cm in diameter The cut surface of the spleen revealed almost confluent infarctions, some anemic and some hemorrhagic in an area 6 by 10 cm in the central portion of the organ The kidneys were markedly hyperemic and both of them showed scattered petechial hemorrhages and anemic infarctions throughout Similar hemorrhages were noted in the mucosa of the bladder The adrenals were not remarkable and the liver showed only slight edema on the cut surface

On opening the cranium, the dura mater was found greatly distended Extensive, recent, subarachnoid hemorrhage covered practically the whole right hemisphere and the base of the entire brain An aneurysm measuring 3 mm in diameter of a distal branch of the right middle cerebral artery was found within the leptomeninges This had ruptured in the area of the foot of the third right frontal gyrus Not only had blood extended into the subarachnoid space from this lesion, but there had been a massive hemorrhage into the substance of the brain extending into the ventricle The area of the hematoma measured 11.5 cm by 6 cm and involved most of the white substance of the right cerebral hemisphere just above the lateral ventricle All ventricles were filled with recently clotted blood In addition, there was a recent aneurysm of the right posterior communicating artery, measuring 3 mm in diameter

Final pathologic diagnoses were (1) Subacute bacterial endocarditis of the mitral and aortic valves with distinct insufficiency of both valves (2) Embolic infarctions of the myocardium, old (3) Mycotic aneurysms of two mesenteric arteries, of the splenic artery, of the distal branch of the right middle cerebral artery, and of the right posterior communicating artery (4) Focal embolic glomerulonephritis

#### SUMMARY AND CONCLUSIONS

We have reviewed the literature on certain aspects of subacute bacterial endocarditis and have reported a case We feel that the following points are noteworthy

- 1 Patients suffering from dental caries with or without pyorrhea are prone to suffer transient bacteremias with *Streptococcus viridans* and other organisms found about the teeth These bacteremias occur spontaneously without the performance of oral surgical procedures, although tooth extractions in such patients have been shown conclusively to precipitate such seeding of the blood stream in a high per cent of cases In patients with cardiac deformities (congenital or rheumatic), such insults may result in subacute bacterial endocarditis

- 2 Given a patient with valvular or congenital heart disease with dental caries or pyorrhea, it would seem best to do three things in the following order (a)

quickly establish adequate sulfonamide blood levels, preferably with sulfadiazine at present, (b) clean up the teeth and gums as much as possible by appropriate dental hygienic measures so as to minimize subsequent wound contamination, and (c) extract the carious teeth, preferably in stages. The drug should be maintained postoperatively until the sockets show evidence that clean healing has been well established. Should the patient in addition be suffering from active rheumatic fever, the regimen might be deferred temporarily to allow the rheumatism to subside. If this failed to occur after a reasonable interval, the above program could justifiably be started, with the full realization, however, that the rheumatic process might be aggravated temporarily by the sulfonamides.

3 A policy of watchful waiting is not reasonable in these patients with structural heart defects and dental caries for the reason that if left alone, the caries becomes worse and transient bacteremias will occur even though the teeth are not touched. Occasionally such patients have been subjected to dental surgery after a bacterial endocarditis has been established (though not recognized) and the tooth extraction has been erroneously regarded as the cause of the disease.

4 Mycotic aneurysms in bacterial endocarditis may rupture and lead to a very large hemorrhage, producing circulatory collapse, shock, profound anemia, i.e., the clinical picture of severe blood loss. When such a hemorrhage occurs in the peritoneal cavity, the circulatory picture may be further complicated by ileus, abdominal distention, signs of peritoneal irritation and marked leukocytosis. Clinically the syndrome may simulate peritonitis, or mesenteric thrombosis or embolism.

5 A case has been reported which illustrates the foregoing points. Adequate sulfonamide therapy for three days before and three days after tooth extraction failed to prevent the occurrence of subacute bacterial endocarditis. (That the bacterial endocarditis had not already been established before the teeth were extracted cannot be conclusively proved. Clinically this seems improbable.) In the course of this illness, the patient developed a massive hemoperitoneum (not previously reported in the literature). The true cause of the hemorrhage (ruptured mycotic aneurysm of the superior mesenteric artery) was not established even at the time of laparotomy, although the bleeding was successfully checked by suturing and the patient recovered, only to succumb a month later to massive cerebral hemorrhage, also from a ruptured mycotic aneurysm.

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### TUBERCULOID LEPROSY A CASE REPORT\*

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At the present time, there seems to be a likelihood that we shall see more cases of leprosy in this country than ever before. It is important to be on the alert for such cases at all times and more so during these times of global warfare and travel. Contrary to what is commonly believed, this disease is not uncommon in the United States. Most of the cases have been seen in the Gulf Coast area, namely, Florida, Louisiana, and Texas, although sporadic examples of the disease have been reported from the whole country<sup>1, 2</sup>. There is a general misconception that this disease is seen only in tropical and semitropical climates. Sutton<sup>2</sup> states that the greatest number of cases in proportion to total population occur in Iceland. The disease is endemic in Mexico, Central and South America. Pardo-Castello and Tiant<sup>3</sup> find that all healthy persons in Cuba are lepromin positive. This, they believe, is because it is a leprosy country and all have been in contact with leprosy persons for many years.

I have only discussed the local prevalence of leprosy to demonstrate that it is not at all uncommon in our front yard. Its geographical distribution is such that our troops will undoubtedly be exposed to it to some extent and we may see an increasing number of cases in the coming years. It is hoped that the presentation of this case will stimulate a greater watchfulness for this disease.

#### CASE REPORT

The patient, a 23 year old male of Japanese parentage, was admitted to the hospital on September 2, 1943 with the diagnosis of tinea circinata. He had noted a skin eruption on his buttocks seven months prior to admission. In the course of a month or two, the eruption had spread to his face, the lateral surface of his left thigh, right arm and forearm, and both hands and feet. It had been moderately pruritic for the first two months but was entirely asymptomatic after that. He had never noted any shooting pains, numbness or tingling in his extremities. He had had a watery nasal discharge when the weather was hot during the past year and a monthly nose bleed during this period. He had never been troubled by purulent nasal discharge.

The patient was born in Baldwin Park on the outskirts of Los Angeles. He had spent three months on one of the Hawaiian Islands in the summer of 1929 and had resided in Japan from 1930 to 1931. Up to the time of induction, 18 months before, he had been a truck gardener.

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His past medical history was entirely non-contributory

His family history did not disclose the presence of any familial diseases. His father was living and well. His mother had died of causes unknown to the patient. One sister was living and well and a brother had died at the age of seven with an undiagnosed fever. The patient had been married for one year. His wife was delivered of a full term healthy infant while he was under observation. She was in good health. No history of any contact with persons suffering with a disease similar to his own could be elicited.

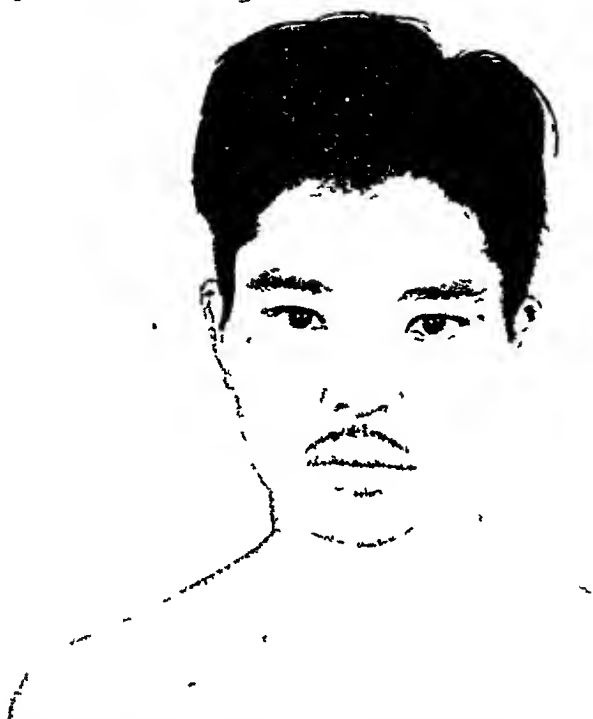


FIG 1 Demonstrates thickening of features suggestive of the leonine facies. The lesions described in the eyebrows and in the zygomatic areas of the cheeks are clearly seen. Photo by U S Army Signal Corps

On admission, the patient weighed 130 pounds and his height was given as 65 inches. The striking feature on examination was the presence of large areas of skin involvement with slightly raised arcuate and festooned borders enclosing areas of slightly thickened, scaling dry skin. The borders measured one to one and a half centimeters in width and consisted of reddish brown, flat-topped papules fused to form a continuous margin. The hairs were present in the involved areas. The smaller lesions were basically similar and consisted of slightly elevated plaques with branny scaling centrally. In the smaller lesions there were no central clear zones.

In general, the distribution of the skin lesions was symmetrical. There was a large area measuring 10 by 15 centimeters involving the adjacent areas of the two buttocks. This was the first lesion. There was a 23 by 30 centimeter figure on the lateral aspect of the left thigh and another 15 by 30 centimeters involving the dorsal and lateral surfaces of the right arm and forearm. There were smaller lesions varying from one to 10 centimeters in diameter scattered in the lateral portions of both



eyebrows, over the right zygomatic region, below the lobe of the right ear; under the right mandible, at the base of the neck posteriorly, on the palmar surfaces of the right thumb and third and fourth fingers, the right thenar and hypothenar eminences, the dorsum of the left hand, the palmar aspects of the left thumb, third and fifth fingers, the left elbow and the lateral aspect of the left arm, the right lateral malleolus and the area just proximal to it, the lateral border of the right foot and the medial surface of that heel, the lateral surface of the left leg and the dorsal surface of the left great toe. The larger areas of skin involvement were hypesthetic or anesthetic to pin prick.



FIG 2 Illustrates the initial lesion noted on the buttocks. Photo by U S Army Signal Corps.

The ulnar and radial nerves were diffusely and uniformly thickened bilaterally to form trunks one centimeter in diameter. Three or four firm, freely movable glands were felt along the course of the thickened ulnar nerve trunk. There were no sensory changes in the areas supplied by these nerves. The right superficial auricular nerve was readily visualized by having the patient look over his left shoulder and was palpable and whipcord-like.

On admission the red blood cell count was 5,700,000 with a hemoglobin of 95 per cent (T) and a white blood cell count of 6350. The differential blood count was polymorphonuclears 58 per cent, lymphocytes 38 per cent, and eosinophiles 4 per cent. The sedimentation rate (Cutler) was 1 millimeter and  $2\frac{1}{2}$  millimeters per hour respectively. The blood Kahn and Wassermann reactions were negative, and the serum total cholesterol was 1482 milligrams per cent. Urine examination showed no abnormalities. Nasal scrapings and ear lobe preparations failed to demonstrate

acid-fast organisms. Skin scrapings revealed no fungi. Roentgenogram of chest was reported as negative and roentgenograms of the hands showed no lesions suggestive of sarcoidosis. Skin tests done with 0.2 cc. of 1 to 10,000 histamine hydrochloride resulted in a 3 centimeter wheal but no zone of erythema in the anesthetic area of the buttock. A similar wheal surrounded by a 0.5 centimeter border of erythema developed when the test was performed just outside the anesthetic area.

A biopsy was taken from the margin of the lesion on the buttocks. The microscopic report was as follows: "There are many small areas of chronic granulomatous inflammation lying in the dermis and extending along the skin appendages into the



FIG 3 Illustrates the lesion described on the lateral aspect of the left thigh  
Photo by U. S. Army Signal Corps

subcutaneous fat. Some of these granulomatous lesions incorporate peripheral nerves. The most striking features of the lesions are the giant cells. The other cells are occasionally epithelioid but many lymphocytes are likewise present. Some of the epithelioid cells are vacuolated and some have almost clear cytoplasm. There is no instance of necrosis. Acid-fast stains controlled by positive tuberculous material and others very lightly decolorized failed to demonstrate acid-fast bacilli. No other causative agent is found. Neither tuberculosis nor leprosy can be excluded.

Another biopsy was taken of the enlarged epitrochlear glands. The microscopic description follows: "The lymph node structure is preserved but there is much desquamation of lining cells into the lymph sinuses and mixed with these cells are small numbers of lymphocytes and leukocytes. Although occasional pale cells are seen

these do not resemble the large globular cells of leprosy. The type of alteration in the lymph node is that commonly designated as reactive or sinus catarrh."

The Army Medical Museum reviewed the sections and gave the following report: "It is our impression that the lesion is leprosy of the tuberculoid type. This is a form of leprosy in which the organisms frequently are not found in the histologic sections."

During the period of observation, the patient remained asymptomatic and there was no evidence of spread or regression of any of his lesions. A complete examination of the eye and its appendages revealed no findings except enlargement of the corneal nerve fibrils on slit lamp study.

### DISCUSSION

The diagnosis of leprosy was suspected on the day of admission. *Tinea circinata* and tuberculids were considered in the differential diagnosis. The presence of the anesthetic skin lesions and the thickened nerve trunks fulfill the criteria of the United States Public Health Service for the diagnosis of leprosy.<sup>2</sup> Manson-Bahr<sup>4</sup> states that leprosy is the only skin disease showing anesthesia. The sedimentation rate was extremely slow. This confirms Manson-Bahr's<sup>4</sup> statement that the sedimentation rate is always decreased in leprosy. The histamine skin test has been suggested by Pardo-Castello and Tiant<sup>3</sup> in determining the state of the nerve supply to the involved areas in patients, especially children, who cannot cooperate in the thermal and pin prick tests necessary. When a solution of histamine is injected into the normal skin a small wheal surrounded by a halo of erythema results. The wheal is due to local action of the histamine on the capillary walls and the erythema is the result of an "axon reflex." When the local nerve endings are destroyed or if the peripheral nerves supplying the area are damaged, the "axon reflex" action is knocked out. Hence, as in our case, the area of erythema was absent when the histamine was injected into the anesthetic area on the buttocks.

Pardo-Castello and Tiant<sup>3</sup> recently presented the South American classification of leprosy into lepromatous, tuberculoid and non-specific types. This classification appeals to me because it is at the same time clinical, pathological and physiological, in contradistinction to the older purely clinical classifications. Furthermore, when cases are classified in this manner, fairly accurate prognostication is made possible.

Our case was classified as tuberculoid before the final biopsy report was returned because of the presence of the characteristic skin lesions described by Pardo-Castello and Tiant<sup>3</sup> as "sharply circumscribed erythematous patches or flat infiltrations, often ring shaped or festooned, with macular centers and elevated border, the latter being uniform or composed of small nodules arranged side by side", the typical pencil-like enlargements of the nerves, the tuberculoid structure described in the first biopsy report and the failure to demonstrate the lepra bacilli. In the older classifications this case may be labeled either as anesthetic or mixed leprosy. In tuberculoid leprosy, the prognosis is good, the patient's immunity is high, he does not excrete bacilli and is, therefore, not dangerous to the community.

## SUMMARY

A case of tuberculoid leprosy is presented. The importance of being on the lookout for this disease as our soldiers return from the far flung corners of the earth is emphasized. A plea is made for the adoption of the South American classification of leprosy.

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**-BLEEDING PEPTIC ULCER IN A YOUNG AVIATION CADET.  
REPORT OF CASE \***

By MAURICE B SIEGEL, 1st Lt, M C, and BERGEIN M OVERHOLT, Capt, M C,  
A U S, F A C P

## INTRODUCTION

THE concept of peptic ulcer as a psychosomatic disease is rapidly gaining ground,<sup>1, 2</sup> and apparently with good reason, as the increased abnormal psychic stimuli created by the advent of the war and the need for adjustment to a new environment are all reflected in the many reports of an appreciable increase in the incidence of dyspepsia and ulcer syndrome. Numerous reports from geographically scattered Army General Hospitals<sup>3, 4</sup> show a 30 to 35 per cent incidence of proved peptic ulcers in admissions to the Gastrointestinal Services of these hospitals. Hurst,<sup>5</sup> in his survey of digestive disorders in the English and French armies, found that whereas gastric disorders were comparatively rare in World War I the symptom complex of dyspepsia presents the largest single type of disease in the modern army. Similar experiences were found in the Royal Navy,<sup>6</sup> Royal Air Force, and Canadian Army.

We present our case for several reasons. *First* after a survey of the literature, this appears to be the first case of a bleeding duodenal ulcer in an aviation cadet who was actively engaged in routine training, including acrobatic spins, rolls, and dives.

*Second* to present several interesting features in this case, (a) the patient had no symptoms while flying, but only felt weak and faint while walking to and from his plane, carrying his parachute pack which weighed approximately 50 pounds, (b) to correlate his flying record as noted by his instructor with the progression of his anemia.

*Third* hemorrhage from a duodenal ulcer in a patient 19 years old is not a very frequent occurrence.

\* Received for publication May 26, 1945

## CASL REPORT

An aviation cadet, age 19, was admitted to the Station Hospital on January 16, 1943 from a nearby primary air force school, for observation and treatment of weakness and pallor, evident for a few days prior to admission.

He stated that for about 10 days preceding his entry into the hospital he felt weak and tired easily, a most unusual situation for him. On January 9 he took a cathartic because he had vague upper abdominal distress, and late that day he had an abrupt bowel movement which was "coal black." He felt faint, dizzy, and perspired freely, but shortly afterwards regained his equilibrium and was able to go back to his studies in the evening. He continued to notice black stools until January 15. During the entire time that he was bleeding, he continued to fly because he desired to graduate with his primary class some 10 days later. On January 11, his friends and associates noticed his pallor, he began to feel weak and listless, tire easily, and barely manage to get to and from the cockpit of his plane, wearing his flying suit and parachute. For three days prior to his admission to the hospital, he was actively engaged in practicing solo acrobatics, such as snap rolls, loops, slow rolls, spins and dives, and at no time during these maneuvers in the air did he experience "black-outs," scotomata, dyspnea, or even feel faint. On January 13 he felt so weak that he fell to the floor upon arising from his bed, and reported to sick call for observation. Two days later he entered this hospital.

On admission we saw a well-developed and well-nourished young white adult male with marked pallor, all the more striking because of his fair complexion making him look almost cadaverous. He was very definite upon questioning that he did not at any time have abdominal pain, other than the slight discomfort experienced on the

TABLE I

Date	Hb (gm)	RBC	Occult Blood
1/16/43	33.2% (5.25 gm)	2,000,000	4+
1/19/43	37% (5.75 gm)	2,500,000	3+
1/20-24/43	40% (6.3 gm)	2,500,000	1+
1/26/43	48% (7.55 gm)	2,900,000	Negative
(ferrous sulfate added to diet at this time)			
2/2/43	59.6% (9.25 gm)	3,110,000	Negative
2/8/43	74.5% (11.55 gm)	3,600,000	Negative
2/15/43	93% (14.45 gm)	4,500,000	Negative

(Hemoglobin determined by photo-electric cell after the method of Peters and Van Slyke, wherein 100 per cent is equivalent to 15.5 gm Hb)

first day that he noticed tarry stools. Physical examination revealed marked pallor of the skin, mucous membranes and nail beds, a heemic systolic murmur, and tachycardia of 100 per minute. Blood pressure was 100 mm Hg systolic and 65 mm diastolic, and the patient stated that he felt faint, dizzy and weak. Laboratory studies showed a hemoglobin of 33 per cent (5.2 gm) and a red blood cell count of 2,000,000. Stool examination showed a 4+ reaction for occult blood. Bleeding and clotting time, platelet count, leukocyte count, differential, and urine examination were entirely normal. The patient was regarded as having a silent bleeding ulcer and started on a modified Sippy routine supplemented with colloidal aluminum hydroxide and tincture of belladonna. On this régime he showed rapid improvement, and as his stools became negative for occult blood, his hemoglobin and erythrocyte count correspondingly rose (table I).

He was confined to his bed for six weeks, and at no time did he exhibit abdominal pain, except in the latter days of his stay in the hospital, when, if he did

not get his milk on time or if it did not contain adequate cream, he would have mild epigastric discomfort, promptly relieved by intake of milk and cream. A gastrointestinal series was performed when all evidence of bleeding had ceased and a deformed, irritable, poorly-filled spastic duodenal bulb was demonstrated. After the stools had become negative for occult blood, ferrous sulfate was given in 5 gr doses three times a day because the rate of rise of his red blood cell count and hemoglobin had slowed down considerably. Following the institution of iron therapy, his hemoglobin promptly rose to 90 per cent and his red blood cell count to 4,500,000.

### DISCUSSION

One can speculate as to whether the life of an aviation cadet, with its particular stresses and strains, was the main causative factor in this bleeding episode, and, if so, whether he should be allowed to resume his flying career. The problem of ulcer in the Army differs from that in civil life in that the trend today is to discharge these ulcer cases because in the long run they are more of a burden to the service and hence are better off under conditions of civil life where dietotherapy can be more carefully followed and attempts can be made at modifying those adverse conditions of stress and strain to which the patient might be subjected.

A rather interesting sidelight on the case has already been briefly mentioned in that this patient with an erythrocyte count of 2,000,000 and a hemoglobin of 32 per cent was able to fly and do acrobatics and not show any dyspnea or anoxia, such as might have been expected with the arterial oxygen saturation so low. The arterial blood of a patient whose hemoglobin is 30 per cent of the normal value will contain only a little over six volumes per cent of oxygen<sup>8</sup> and hence, in order to compensate the circulation rate (cardiac output) is increased, each unit of blood giving up a smaller part of its oxygen load than normal to the tissues, so that the venous blood has the same relative percentage of oxygenation as normally. It would appear that physiologically he had adjusted to his new low blood level and was able to carry on his flying activities. However, his proficiency as gauged by his flight instructor was markedly impaired and he was given three consecutive unsatisfactory check flights something that had not happened previously at any time during his training period. They stated that he showed improper coordination, poor judgment and increased tenseness during those flights while he was bleeding actively. Previous to that time he had received average satisfactory ratings for his flights.

### SUMMARY

1 We have presented a case of bleeding peptic ulcer in a young air cadet actively engaged in routine flight training. To our knowledge this is the first such case to be reported in the literature.

2 The ability of the patient to continue to fly in spite of a rather profound anemia has been stressed, although it would appear that his flying efficiency was impaired in proportion to the degree of anemia.

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### CARCINOMA OF THE UMBILICUS METASTATIC FROM CARCINOMA OF THE STOMACH \*

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CARCINOMA of the umbilicus, either primary or occurring by metastasis has seldom been reported, but has long been known to occur. Osler,<sup>1</sup> in the first edition of his textbook, speaking of cancer of the stomach, stated "Occasionally, a secondary metastatic growth occurs subcutaneously, either at the navel or beneath the skin in the vicinity. In an instance recently under observation in a patient with jaundice, which developed somewhat suddenly and was believed to be catarrhal, there were no signs of enlargement of the liver or tumor of the stomach, but a nodular body developed at the navel, which on removal proved to be typical scirrhus carcinoma. A second case in the ward at the same time, with an obscure doubtful tumor in the left hypochondria, developed a painful nodular subcutaneous growth midway between the navel and the left margin of the ribs." Alvarez<sup>2</sup> also called attention to examination of the umbilicus for metastasis from gastric cancer, and recently Walters, Gray, and Priestly,<sup>3</sup> referring to carcinoma of the stomach, stated "In an occasional case, a metastatic nodule may be palpated or even seen in the umbilicus. When present, this nodule is characteristic of carcinoma and can hardly be mistaken for any other type of lesion. The umbilicus may be discolored a dusky bluish red (figure 31)." The condition, however, is evidently quite rare and recently Alvarez<sup>4</sup> has written us as follows: "I am sure that obvious metastasis to the umbilicus is rare. I remember seeing only one striking case in years. As I remember, in that case, the man had a tumor around the navel as big as a door-knob before he had any symptoms of indigestion" (Dec 21, 1942). Metastasis to the umbilicus in cases of carcinoma of the stomach is thus apparently a rather uncommon finding, but when a tumor mass does occur there, it should be suspected to be secondary to malignancy within the abdomen and especially in the stomach. Primary cancer of the umbilicus is by far more uncommon than is the metastatic form.

Cullen,<sup>5</sup> in his monograph on the umbilicus, a large and exhaustive treatise, collected 27 cases of carcinoma of the umbilicus secondary to carcinoma of the

\* Received for publication October 23, 1943.

stomach, including one of his own. It is our impression that he thoroughly reviewed the medical literature up to that time. Warner<sup>6</sup> reported an additional case in a man aged 54 together with a case of carcinoma of the rectum with metastasis to the umbilicus. Witthauer<sup>7</sup> reported six cases of carcinoma of the stomach in which metastasis to the umbilicus was present. The ages were 17 (1), 23 (1), 27 (1), 41, 48 and 61 years. The umbilicus was frequently blue-red or bluish in color and in some, merely a hard tumor was felt. In some instances Witthauer believed that carcinomatous emboli into persistent paraumbilical veins took place, in others, direct local extension through the peritoneum to the subcutaneous tissue of the umbilicus probably occurred and in others the mode of extension was apparently by metastasis through lymphatic and blood vessels. In one case, a man aged 41, only in the umbilicus was there any evidence of metastasis, even upon operative exploration. He lived nearly a year following partial gastrectomy before dying as a result of metastasis. Hartmann<sup>8</sup> reported one case of carcinoma of the umbilicus in a man, secondary to carcinoma of the stomach. The lesion had a raised border, was slightly ulcerated in the center and was of hard consistency. It proved to be adenocarcinoma upon microscopic examination. Including Osler's<sup>1</sup> case and the one illustrated in Walters, Gray and Priestly's text,<sup>3</sup> there have been 37 cases of carcinoma of the umbilicus metastatic from cancer of the stomach reported. We wish to report one additional case.

#### CASE REPORT

A white woman, aged 44, was first seen by one of us (L. E. L.) on September 21, 1942 and was admitted to St. Mary's Hospital. Her past history was unimportant. She was extremely nervous and complained of migratory pains in the back and neck. For about a year prior to her admittance to St. Mary's Hospital, she had a gradual loss of appetite, mild pains in the epigastrium, gaseous distention of the stomach and occasional nausea after meals. She had lost weight progressively. She had been examined in a hospital in California in April, 1942 where a diagnosis of peptic ulcer of the stomach had been made. She was treated medically and improved considerably. Roentgenographic examinations were made in California in June, and she was told that there was a marked improvement in her condition. About this time she began to notice a peculiar hardness of the umbilicus which gradually became rather tender. Her nervousness increased and vague pains developed in her back and neck.

The physical examination revealed a poorly nourished woman who was extremely nervous and complained of fleeting pains through her back and neck. There was slight tenderness in the occipital region extending down into the posterior cervical region. The eyes were normal and the ears, nose and throat were not remarkable. There was no adenopathy or rigidity of the neck although there was some muscle spasm on pressure over the posterior cervical area. The chest was symmetrical, expansion was equal, voice and breath sounds were normal and there were no râles. The breasts were slightly atrophic and pendulous but showed no masses. The apex beat of the heart was palpable in the left fifth interspace; the sounds were regular and rhythmic with no murmurs. The abdomen was scaphoid and showed no rigidity. There was some tenderness in the right hypochondrium extending down into the right lower quadrant. There was a suspicious mass in the upper abdomen which was movable and felt rather hard. The umbilicus presented a prominent, frosted-appearing induration about 2.5 cm. in diameter. There was also a very



of induration around the navel apparently beneath the skin approximately 2 cm beyond the umbilicus. The genitalia were normal. The pelvic examination revealed a small freely moveable anteфлекed uterus. The adnexa were normal on palpation. The upper and lower extremities showed no atrophy or edema.

The blood count showed hemoglobin, 100 per cent (14.5 gm Hb), erythrocytes, 5.05 millions, leukocytes, 5,200 per cu mm, neutrophils, 69 per cent (one non-filament); lymphocytes, 26 per cent, eosinophiles, 2 per cent, basophiles, 3 per cent. A specimen of urine was normal except for a faint trace of albumin. The Kolmer Wassermann, and Kahn reactions on the blood serum were negative.

Roentgenographic examination showed no disease in the heart and lungs. No cardiospasm or signs of gastric retention were found but there was a suggestion of a small ulcer on the lesser curvature of the stomach about two inches (5 cm) above the pylorus. The stomach and duodenum were very irritable and the roentgenologist (Moreton J. Thorpe, M.D.) stated "It is possible that the extreme nervousness (of the patient) is responsible for all the duodenal and gastric irritability, but also there is a very strong suspicion of a gastric ulcer. If the patient could be quieted down, reexamination might be warranted." Roentgenographic examination of the spine disclosed normal vertebrae. In view of the semihysterical condition of the patient, a gastric analysis was not attempted.

On September 28, 1942 a biopsy was removed from the central portion of the umbilicus under local anesthesia. Histological examination of this biopsy showed adenocarcinoma, grade IV, involving the skin of the umbilicus. It was the impression of the pathologist (L. P.) that the tumor was probably of gastrointestinal origin, because of the presence of occasional signet-ring type cells distended with mucus which were seen among the tumor cells. On October 2, 1942 an exploratory laparotomy (by L. E. L.) was performed. The omentum was adherent to the umbilicus and an area of nodular masses could be felt in the parietal peritoneum. The omentum was studded with metastatic nodules of carcinoma, particularly near its gastric attachment. The stomach revealed an extensive scirrhous cancer involving the pyloric half which completely encircled the distal third. A number of hard tumor nodules were felt in the parietal peritoneum near the umbilicus and in the gastrohepatic ligament. The gall-bladder and duodenum were normal.

The postoperative condition of the patient was poor, she became gradually weaker and died November 11, 1942, apparently from bronchopneumonia. Permission for an autopsy was refused.

### SUMMARY

1 A case of metastatic involvement of the umbilicus from inoperable carcinoma of the stomach, apparently the thirty-eighth reported in the medical literature, is presented.

2 It is believed that such cases are not so rare as the literature indicates and more careful examination of the umbilicus for metastasis in suspected cancer of the stomach is recommended.

We are indebted to Miss Florence L. Wickes, Reference Librarian, Lane Medical Library, Stanford University School of Medicine, San Francisco, for her assistance.

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## CORRECTION

### DOSAGE OF ACETYL-BETA-METHYL-CHOLINE CHLORIDE

In the article by Captain Julius R. Pearson and Lt. Colonel Albert W. Wallace, "The Syndrome of Paroxysmal Tachycardia with Short P-R Interval and Prolonged QRS Complex, with Report of Two Cases," in the ANNALS OF INTERNAL MEDICINE, 1944, Volume 21 (November), page 838, it is stated "he was given 0.2 gm. acetyl-beta-methyl-choline chloride subcutaneously." This figure (which was a typographical error in the manuscript) should read 0.02 gm. The larger quantity would be a dangerous overdose. We are indebted to the Medical Department of Merck and Co., Inc., for calling attention to this oversight.

## EDITORIAL

### *THE SITE OF ANTIBODY FORMATION*

THE problems concerned with the formation of antibodies have stimulated the interest of investigators for many years. One of the most interesting of these concerns the site of antibody formation and the types of cells concerned in the process. Is this a general property of all or most of the cells of the body, or is it restricted to certain special types of cells? In spite of a great deal of speculation and study, relatively little direct evidence in answer to these questions has been obtained.

Since the observations of Metschnikoff and his followers over 50 years ago attention has been centered largely on the cells of the reticuloendothelial system. The fact that the macrophages as well as the polymorphonuclear neutrophilic leukocytes engulf and digest bacteria and other foreign cells as well as absorb certain foreign substances in colloidal suspension naturally suggested that these cells are also concerned in the elaboration of the specific antibodies which subsequently appear in the circulation. Although phagocytosis and digestion of foreign cells by the reticuloendothelial cells is easily demonstrable, there is little or no direct evidence of antibody production by them. Considerable indirect evidence for this has been advanced, however.

Some observers have reported that following an injection of antigen, antibodies appeared in higher concentration in the spleen and bone marrow than in the blood. Removal of the spleen (in guinea pigs, and dogs) a few days after injection of an antigen reduced significantly the antibody titer subsequently attained by the animal, as compared with nonsplenectomized control animals. Topley<sup>1</sup> showed that if the spleen from a rabbit so treated is ground up and injected into a normal rabbit, the latter will develop antibodies (in low titer) which appear and disappear more rapidly than in an animal primarily inoculated with the antigen. Furthermore such an animal will not show an accelerated response to a subsequent injection of the same antigen. This suggested to Topley that the reticuloendothelial cells in the splenic tissue injected did not liberate antigen which could act on the cells of the new host, but that the antibodies which appeared in the latter were produced in and liberated by the reticuloendothelial cells in the splenic pulp which had been injected.

One of the principal arguments which has been advanced in support of the view that the reticuloendothelial cells are the site of antibody formation is the effect produced by "blockade" of the reticuloendothelial system. If an animal is injected intravenously with India ink or some suitable material in colloidal suspension the reticuloendothelial cells generally become

<sup>1</sup> TOPLEY, W. W. C. Role of spleen in production of antibodies. *Jr. Path. and Bact.* 1930, XXXIII, 339-351.

engorged with this material. If an antigen is then injected, there may be a partial or complete lack of antibody formation which is commonly attributed to the preoccupation of the reticuloendothelial cells with the colloidal particles previously administered.

Sabin<sup>2</sup> made some interesting observations on the behavior of macrophages which had ingested visible aggregates of a dye-protein, which have been advanced in support of the view that the macrophages produce antibodies. In supravital preparations she observed the gradual removal of the dye from these particles, and the disappearance of the protein particles which presumably had gone into solution in the cytoplasm. Also after these particles had disappeared and at a time when antibodies were appearing in the blood, she observed shedding of fragments of the cytoplasm by the macrophages without apparent injury to the latter, which she interpreted as an excretion or expulsion of antibody by the cell. There is, however, no direct evidence that these fragments contained antibody. Furthermore, as this phenomenon was not observed in perfectly fresh preparations, the possibility seems not excluded that this represents an early manifestation of cell degeneration rather than a physiological mechanism. A similar shedding of cytoplasm by lymphocytes has been described (Downey and Weidenreich).

Attempts have been made to demonstrate antibody formation in tissue cultures. The most convincing results have been obtained by cultivation of tissues taken from animals which had been previously injected with antigen. Thus (among others) Meyer and Loewenthal<sup>3</sup> demonstrated the formation of agglutinins for typhoid bacilli in cultures of the spleen, lymph nodes and milk spots of the omentum of rabbits which had been injected with typhoid bacilli. The experiments previously discussed were not so designed as to determine which cells in the tissues examined produced the antibody demonstrated. Since the milk spots, however, are stated to contain only reticuloendothelial cells and a few fibroblasts, this appears to be the most direct evidence available of the formation of antibodies by reticuloendothelial cells.

Relatively little attention has been devoted in the past to the part lymphocytes may play in the defense mechanism. Unlike the reticuloendothelial cells and the neutrophilic leukocytes, they are not phagocytes. For many years, however, Bunting<sup>4</sup> in particular has maintained that the lymphocytes play an important rôle in the defense against toxins and soluble antigens. The evidence for this, also, has been largely indirect. When toxins gain access to the body tissues, they are largely taken up into the lymph and pass into and through the regional lymph nodes where they appear to be ab-

<sup>2</sup> SABIN, F. R. Cellular reactions to a dye-protein with a concept of the mechanism of antibody formation, *Jr Exper Med*, 1939, **1x**, 67-82.

<sup>3</sup> MEYER, K., and LOEWENTHAL, H. Untersuchungen über Antikörperbildung in Gewebekulturen, *Ztschr f Immunitätsforsch u exper Therap*, 1928, **liv**, 409-419.

<sup>4</sup> BUNTING, C. H. Cell reactions in resistance and immunity, *Wisconsin Med Jr*, 1925, **xvii**, 305-308.

sorbed or filtered out to a greater or lesser extent. In high concentrations they may cause necrosis of the cells in the nodes, but in lesser concentration, under conditions more favorable to the host, they stimulate a proliferation of the lymphocytes which is coincident with the development of antibodies. In acute infections, during the early stage there is usually an increase in granulocytes and an actual reduction in lymphocytes. In cases with a favorable outcome, however, there is often a well marked lymphocytosis as recovery sets in, approximately coincident with the appearance of antibodies in the circulation. In chronic infections like tuberculosis, a lymphocytosis is common in patients whose disease is running a favorable course, whereas an increase in monocytes at the expense of the lymphocytes suggests an active progressive infection.

Bunting also believes that the distribution of lymphocytes in inflammatory lesions indicates their importance in the defense mechanism. "The position of the normal lymphoid accumulations, the grouping of lymphocytes which are nonphagocytic cells, about the tubercle, the gumma and acute inflammatory foci, forming a protective ring through which toxins must filter before reaching vital tissues, the curve of reaction in diseases followed by immunity, all these point toward a chemical function for the cell."<sup>4</sup>

Procedures such as exposure to roentgen-ray which destroy lymphoid tissue, diminish resistance and lower antibody production in animals. On the contrary, if lymphoid tissue is stimulated by exposure of animals to dry heat, antibody production is greater than normal.

More direct evidence of the formation of antibodies in lymph nodes was furnished by McMaster and Hudack.<sup>5</sup> They injected bacterial 'vaccine' intradermally into the ears of mice, and several days later demonstrated antibodies in the regional lymph nodes in higher concentration than in the blood. That this was not due to a concentration in the lymph nodes of circulating antibody which had been formed elsewhere was proved by injecting different types of vaccine into the two ears of the same mouse. Then the regional lymph node contained antibodies for the organism injected into the homolateral ear, and none or much smaller quantities of antibody for the species injected into the opposite ear.

Ehrich and Harris<sup>6</sup> made similar studies in rabbits, injecting typhoid vaccine into the foot pad on one side, and sheep erythrocytes on the other. They were able to examine the afferent and efferent lymph as well as the regional node itself. They observed well marked hyperplasia of the lymphocytes in the node and a marked rise in the cell count of the efferent as compared with the afferent lymph (about 5,000 to 67,000), over 99 per cent of which were lymphocytes. After two to four days antibodies ap-

<sup>5</sup> McMASTER, P. D. and HUDACK, S. S. The formation of agglutinins in lymph nodes, *Jr Exper Med.*, 1935, **111**, 783-805.

<sup>6</sup> EHRLICH, W. E. and HARRIS, T. N. The formation of antibodies in the popliteal lymph nodes in rabbits, *Jr Exper Med.* 1942 **131**, 335-357.

peared in the efferent lymph, in much higher concentration than in the afferent lymph and at first higher than in the blood, whereas they found none or only small amounts of antibody for the antigen injected into the contralateral foot

In a more recent study, Harris et al.,<sup>7</sup> have secured more direct evidence as to the part played by the lymphocytes in this reaction. From rabbits injected as in the preceding study they obtained efferent lymph and removed the lymphocytes from the lymph by centrifugalization. They then compared the antibody titer in the lymph and in extracts of the leukocyte sediment. The titer of the latter was consistently greater than that of the lymph, in most cases from two to eight times higher. By appropriate control tests it was shown that the lymphocytes tend to give up antibodies to the lymph in which they are suspended. On the other hand, they could detect no absorption or adsorption by the lymphocytes of antibodies present in the lymph, either in vivo or in vitro.

This evidence of the formation of antibodies by lymphocytes seems convincing. Obviously it does not exclude the possibility of their production by macrophages as well. Ehrich,<sup>8</sup> however, has pointed out that the latter possibility is based on inferences only, and not on direct proof. He suggests that the facts which are known regarding the activities of the macrophages are equally in harmony with the theory that the latter serve to engulf and digest the foreign antigen and so alter it that it can be utilized by the lymphocytes in the actual process of antibody production.

This new work is interesting in directly demonstrating the importance of the lymphocyte in protecting the body from infection. Without doubt the macrophage, the granular leukocyte and the lymphocyte should be regarded as a team, of substantially equal importance, whose coordinated activities are essential for effective defense against infection.

<sup>7</sup> HARRIS, T. N., GRIMM, E., MERTENS, E., and EHRLICH, W. E. The rôle of the lymphocyte in antibody formation, *Jr Exper Med*, 1945, **LXXXI**, 73-83.

<sup>8</sup> EHRLICH, W. E., and HARRIS, T. N. The site of antibody formation, *Science*, 1945, **ci**, 28-31.

## REVIEWS

*Röntgen Treatment of Diseases of the Nervous System* By CORNELIUS G. DYKE, MD, F.A.C.R., and LEO M. DAVIDOFF, MD, F.A.C.S. 198 pages, 24 x 15.5 cm. 1942. Lea and Febiger, Philadelphia. Price \$3.25

In a small volume the authors present a concise review and summary of radiation therapy of neoplasms attacking the central nervous system. The various types of new growths are considered, and in a few brief statements, all the significant literature pertaining to each kind of tumor is summarized. Following this, Drs. Dyke and Davidoff present their experiences in radiation therapy to the different lesions. They not only include the results of other workers and themselves but state the important details of treatment, such as voltage, target-skin distance, milliamperage and filtration uses by each therapist.

Numerous case histories are recorded, which leave no doubt but that favorable results are to be expected following radiation therapy in medulloblastomas, gliomas of the optic chiasm, xanthomatosis, and a few primary spinal extradural sarcomas. Of still more interest than the preceding information are the findings of the authors that certain kinds of tumors long believed to be radio-resistant will often respond to deep roentgen-rays. Hope can now be extended to those patients who are harboring cranio-pharyngiomas, chromophil adenomas, and neurofibroma of the spine.

Prophylactic radiation of the spinal cord is advocated as a routine regime when medulloblastomas and ependymomas are diagnosed, even in the absence of clinical spinal involvement. In the doses suggested, no harm is likely to ensue from the treatments and silent metastases may be eradicated.

Considering the importance of the field covered and the clear method of presenting the material anyone who reads this small volume will be adequately compensated for the effort.

D. J. B.

*Atlas of the Blood in Children* By KENNETH D. BLACKFAN, M.D., and LOUIS K. DIAMOND, M.D. 320 pages, 28 x 20.5 cm. 1944. Commonwealth Fund, New York. Price, \$12.00

The text consists of brief but complete descriptions of the various disease entities. The more important hematological disorders encountered in children are all included with illustrative case reports and a selected bibliography. For simplicity it is divided into (1) The Blood Cells (2) The Erythrocytes in Anemia (3) The Leukocytes in Disease (4) Leukemia (5) Platelets.

The 70 plates are beautifully done by the pediatrician and artist, Dr. Leister. With each plate there is an accompanying key illustration which accurately describes it.

The Atlas is written and arranged with such simplicity that reading is very enjoyable and readily assimilated. It is a real tribute to Dr. Blackfan and to the many fine publications that he and Dr. Diamond have jointly made.

W. M. S.

## BOOKS RECEIVED

Books received during December are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.



- Atlas of the Blood in Children* By KENNETH D BLACKFAN, M D, and LOUIS K DIAMOND, M D 320 pages, 28 × 20.5 cm 1944 Commonwealth Fund, New York Price, \$12.00
- The Embryology of Behavior* By ARNOID GESELL, M D 289 pages, 23.5 × 16 cm 1945 Harper & Brothers, New York Price, \$5.00
- The Pathology of Internal Diseases* 4th Edition By WILLIAM BOYD, M D, LL D M R C P, Ed, F R C P, Lond, Dipl, Psych, F R S C 857 pages, 24 × 15.5 cm 1944 Lea & Febiger, Philadelphia Price, \$10.00
- Endocrinology of Women* By E C HAMBLEY, B S, M D, F A C S 571 pages, 26 × 17 cm 1944 Charles C Thomas, Springfield, Illinois Price, \$8.00
- Textbook of Medical Treatment* 3rd Edition By VARIOUS AUTHORS Edited by D M DUNLOP, B A (Oxon), M D, F R C P (Edin), M R C P (Lond), L S P DAVIDSON, B A (Camb), M D, F R C P (Edin), F R C P (Lond), and J W McNEE, D S O, D Sc, M D (Glas), F R C P (Edin), F R C P (Lond) With a foreword by the late PROFESSOR A J CLARK, B A (Camb), M D, D P H, F R C P (Lond), F R S 1218 pages, 22 × 14.5 cm 1944 Williams and Wilkins Company, Baltimore Price, \$8.00
- American Medical Practice in the Perspectives of a Century* By BERNHARD J STERN, Ph D 156 pages, 21.5 × 14 cm 1945 Commonwealth Fund, New York Price, \$1.50
- Medical Uses of Soap* Edited by MORRIS FISHBEIN, M D 182 pages, 23.5 × 15.5 cm 1945 J B Lippincott Company, Philadelphia Price, \$3.00
- Medical Diseases of War* By SIR ARTHUR HURST M A, D M, F A C P With the cooperation of H W BARBER, M A, M B, F R C P, H B F DIXON, M C, M D, D T M and H, F R C P, E H R HARRIES, M D, F R C P, D P H, F A KNOTT, M D, F R C P, MELVILLE D MACKENZIE, M D, D T M and H, T A ROSS, M D, F R C P, and ARNOLD W STOTT, M A, F R C P 511 pages, 22 × 14.5 cm 1944 Williams and Wilkins Company, Baltimore Price, \$6.00
- Etiology, Diagnosis and Treatment of Amebiasis* By CHARLES F CRAIG, M D, Colonel U S Army, retired 332 pages, 24 × 16 cm 1944 Williams & Wilkins Company, Baltimore Price, \$4.50
- The Story of a Hospital The Neurological Institute of New York, 1909-1938* By CHARLES A ELSBERG, M D 174 pages, 19.5 × 13 cm 1944 Paul B Hoeber, Inc, New York Price, \$3.50
- Lead Poisoning* By ABRAHAM CANTAROW, M D and MAX TRUMPER, Ph D 264 pages, 23.5 × 16 cm 1944 Williams & Wilkins Company, Baltimore Price, \$3.00
- The British Journal of Surgery* Special Issue Penicillin in Warfare Chairman of Editorial Committee GEORGE E GASK (London) 224 pages, 25.5 × 18.5 cm 1944 (Supplement to Vol XXXII, no 125, of the British Journal of Surgery, July 1944) Williams and Wilkins Company, Baltimore Price, \$2.50, paper cover, supply limited
- The Reticulo-Endothelial System in Sulfonamide Activity* By FRANK THOMAS MAHER, Ph D 232 pages, 27.5 × 20.5 cm 1944 University of Illinois Press, Urbana, Illinois Price, \$2.50 paper bound, \$3.00 cloth bound

## COLLEGE NEWS NOTES

### NOMINATIONS FOR A C P ELECTIVE OFFICES, 1945-46

In accordance with the By-Laws of the American College of Physicians Article I, Section 3, the following nominations for the elective offices, 1945-46, are herewith announced and published

<i>President-Elect</i>	Brigadier General Hugh J Morgan, Washington, D C
<i>First Vice-President</i>	Dr James J Waring, Denver, Colorado
<i>Second Vice-President</i>	Dr A B Brower, Dayton, Ohio
<i>Third Vice-President</i>	Dr T Homer Coffen, Portland, Oregon

The election of nominees shall be by the Fellows of the College at its Annual Business Meeting, St Louis, Mo, May 5, 1945 The above nominations do not preclude nominations made from the floor at the Annual Business Meeting itself Nominations for members of the Board of Regents and members of the Board of Governors will be presented at the Annual Business Meeting

Respectfully submitted,

FRANCIS G BLAKE, New Haven, Conn

ROBERT O BROWN, Santa Fe, N M

JOHN H MUSSER, New Orleans, La

JOHN W SCOTT, Edmonton, Alberta

WALTER W PALMER, *Chairman*, New York, N Y

COMMITTEE ON NOMINATIONS

### ADDITIONAL MEMBERS ON ACTIVE MILITARY DUTY

The following additions of members of the American College of Physicians on active military duty in the Medical Corps of the Army, Navy and Public Health Service are herewith recorded Previously reported were the names of 1721 members, which brings the gross number now to 1,845

Ashe, William Francis, Jr	Conway, William Hynes
Atwater, John Spencer	Cook, Joseph Russell
Autry, Daniel Hill	Coombs, Frederick Stanley, Jr
Baldwin Robert Sherman	Darnall, Charles Milton
Barnum, Glenn Lewis	Davie, John Holmes
Bean, William Bennett	Davis, Hal
Bell James Roeder	Drake, Ellet Haller
Bortz, Donald Worcester	Dunham Charles Little
Boyer, Norman Howard	Durkin John Keenan
Brewen Stewart Ferdinand	Everett, Peter, III
Brownley, Harvey Christian	Finkelstein, David
Brownstein Samuel R	Flynn, Joseph Eugene
Brumm, Harold J	Friedland, Elmer
Cain, James Clarence	Friedman Maurice Harold
Callaway James Willis	Friend, Dale G F
Chapman, William Holmes, Jr	Frisch Robert Abraham
Cheskin, Louis Joseph	Frist, Thomas Fearn
Cogan Michael Aaron	Geddis, James Thomas J

The Hospital for Joint Diseases, 1919 Madison Ave., New York City, announced recently its desire to obtain House Staff appointments to fill twelve places on the General Rotating Service. Eight interns are desired to begin July 1, August 1, September 1, and October 1, 1945, each for a nine months' period. One-half of the number appointed may be permitted to continue for another nine months as Junior Residents, and thereafter, one-half of the number of Junior Residents may be continued for another nine months as Senior Residents, in accordance with the Allocation Plan of the Procurement and Assignment Service.

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Major Sidney Schnur, (MC), AUS, (Associate), who preceding the war was a physician in Houston, Tex., has been cited for meritorious conduct with the 7th Bombardment Group and India Task Force from May, 1942, through August 27, 1943. The citation was signed by General Joseph Stilwell, and the Bronze Star, eighth ranking War Department medal, was awarded Major Schnur. The citation read: "Major Schnur showed great initiative, ingenuity and ability in maintaining the health of the command. By successfully raising the sanitation level of the Air Force field installations to an unusual degree, by initiating and following through a malaria control program which has actually controlled the disease, by persistent efforts and novel procedures in the control of venereal diseases, by improving the quality of food served in field messes through introduction of new methods of procurement and distribution, by devising and supplying escape first aid kits to combat personnel, and by his continuous research in various fields of aviation medicine, Major Schnur lowered the noneffective rate from disease to a bare minimum. Major Schnur's devotion to duty and his successful and tireless efforts in the fields of health, hygiene and sanitation reflect great credit on the Armed Forces of the United States."

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Colonel William S. Middleton, (MC), AUS, F A C P, Consultant in Medicine in the European Area, was one of the eight alumni of the University of Pennsylvania to receive special recognition for "outstanding service to the University during the recent past" at Founder's Day meeting of the University on January 20, 1945.

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Major General George F. Lull, (MC), USA, F A C P, Deputy Surgeon General, delivered the commencement address of the Southwestern University Medical School, Dallas, Tex., recently.

Pointing out that treatment and evacuation of wounded must go hand in hand, General Lull described how the problem of saving lives varies in different theaters of war. He contrasted the carefully planned, smoothly regulated chain of evacuation from the Normandy Beachhead with the difficulties under which wounded were evacuated in some Southwest Pacific areas where "small portable hospitals had to be carried forward over mountain trails through jungle to the rear of the fighting troops" and "cases were operated on in the jungle and had to be carried for miles until they could be placed in jeeps."

The reasons for lower mortality rates compared to World War I may be charged to three things, General Lull said: better surgery, done earlier, blood plasma, and chemotherapy. In connection with the latter he stated that the results of the so-called sulfa drugs have been much more spectacular in medicine than in surgery, and cited the lowering of the mortality rate for cerebrospinal meningitis of meningococcal origin to less than one-fourth what it was in World War I, and that of pneumonia.

from 35 per cent in the last war to under 1 per cent. Penicillin, too, he said, had proved its worth in many types of medical cases, notably in the venereal diseases. "Of course," he added, "one of the most important functions of the Medical Department is the prevention of disease. Great strides have been made in this field during the present war."

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The following promotions in the Medical Corps of the Army have been announced:

*Lieutenant Colonel to Colonel*

Oscar Blitz, (Associate), New Orleans, La.

Hugh Richmond Gilmore, Jr., F A C P, Emlenton, Pa.

*Major to Lieutenant Colonel*

Clarence L. Gardner, Jr., F A C P, Aurora, Ill.

Charles E. Lemmon, F A C P, Detroit, Mich.

Joseph O. Weilbaecher, Jr., F A C P, New Orleans, La.

James S. McQuiston, F A C P, Cedar Rapids, Iowa.

David Robert Sacks, F A C P, San Antonio, Tex.

John Mitchell Willis, Jr., F A C P, Philadelphia, Pa.

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The Dallas Southern Clinical Society will hold its fifteenth annual conference at Hotel Adolphus, Dallas, March 19-22, 1945. Among guest speakers will be Dr. George W. Thorn, F A C P, Boston, Medicine; Dr. Charles A. Doan, F A C P, Columbus, Medicine; Dr. J. Arnold Barger, F A C P, Rochester, Minn., Gastro-Enterology; Dr. William H. Sebrell, Jr., F A C P, Washington, D. C., Basic Science.

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Dr. Robert H. Felix, F A C P, Washington, D. C., is President-Elect of the Medical Correctional Association. He has also been appointed Medical Director in charge of the Mental Hygiene Division, Bureau of Medical Service, U. S. Public Health Service, succeeding Dr. Lawrence Kolb, F A C P, retired.

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Dr. Virgil P. Sydenstricker, F A C P, Augusta, Professor of Medicine at the University of Georgia School of Medicine, has been commissioned with the United Nations Relief and Rehabilitation Administration as Chief Counsel in Nutrition for Western Europe. He holds the rank of Colonel, and will have charge of organizing the health service of all nations west of the Balkans.

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Dr. Carroll Lockard, F A C P, Baltimore, is President of the Medical and Surgical Faculty of Maryland, the state medical society.

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Under the presidency of Dr. Victor Schulze, F A C P, San Angelo, and the secretaryship of Dr. Walter B. Whiting, F A C P, Wichita Falls, the Texas State Heart Association will meet at Galveston May 7.

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Dr. William S. McEllroy, F A C P, Dean of the University of Pittsburgh School of Medicine, has been appointed medical survey advisor, succeeding General C. J. ...

R Reynolds, F A C P , of Harrisburg, who resigned to become a member of the staff of the American College of Surgeons Dr. McEllroy will be called upon to advise the Pennsylvania Selective Service Headquarters on various phases of the Medical Survey Program

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Dr Walter L Bierring, F A C P , Des Moines, State Health Commissioner for Iowa, spoke at the dedication of the Raymond Blank Hospital for Children in Des Moines on December 3 This hospital is the first constructed in Iowa exclusively for the treatment of children

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Dr Clarence E Hufford, F A C P , Cleveland, was recently made President of the Ohio State Radiological Society

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#### DR CHARLES A DOAN APPOINTED DEAN, OHIO STATE UNIVERSITY

Dr Charles A Doan, F A C P , who has served since 1936 as Chairman of the Department of Medicine at Ohio State University College of Medicine, Columbus, has been appointed Dean Dr Doan graduated in medicine from Johns Hopkins University School of Medicine in 1923 He went to Ohio State University in 1930 as Professor of Medicine and Director of the Department of Medical and Surgical Research

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Dr Warfield T Longcope, F A C P , Professor of Medicine, Johns Hopkins University School of Medicine, Baltimore, delivered the first John Auer Lecture at the St Louis University School of Medicine, November 29, his title being "Allergic and Toxic Reactions of the Sulfonamide Drugs"

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Dr William W Herrick, F A C P , Professor of Clinical Medicine, Columbia University College of Physicians and Surgeons, and Attending Physician to the Presbyterian Hospital, has been elected President of the New York Academy of Medicine for a term of two years Dr Herrick has had a distinguished career He was one of the early Fellows of the American College of Physicians and at one time served on its Board of Regents

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Dr Edward Kupka, F A C P , has accepted an appointment as Medical Director of the La Vina Sanatorium, La Vina, Calif, and of the Hastings Foundation for Tuberculosis Research, Pasadena, to succeed Dr Carl R Howson F A C P , resigned

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Dr James Howard Means, F A C P , Jackson Professor of Clinical Medicine at Harvard Medical School, Boston, recently addressed the Baltimore City Medical Society on "Hyperophthalmopathic Graves' Disease"

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Dr George W McCoy, F A C P , New Orleans, and Colonel Thomas T Mackie, (MC), AUS, F A C P , New York, have been elected Vice President and Treasurer, respectively, of the American Academy of Tropical Medicine

Dr Philip Levine, F A C P, Linden, N J delivered the first Reginald Knight Smith Lecture at Mount Zion Hospital, San Francisco, January 11 on "Rh Factor and Its Clinical Significance" The lectureship has been inaugurated in memory of the late Dr Smith, who was Chief of the Division of Obstetrics at the Mount Zion Hospital from 1909 to 1937

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Commander F J Braceland, (MC), USNR, F A C P, Psychiatry Branch of the Professional Division of the Bureau of Medicine and Surgery has been appointed an examiner on the American Board of Psychiatry

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Colonel John Minor, (MC), AUS, F A C P, formerly Chief of the Medical Service at the Woodrow Wilson General Hospital, Staunton, Va, is now Consultant in Medicine to the Third Service Command, Baltimore

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Dr Ward Darley, F A C P, is Director of the Rheumatic Fever Diagnostic Service established recently by the Denver Area War Chest The objective is to locate cases of rheumatic fever and rheumatic heart disease among children and to have them referred to proper sources for care The Diagnostic Service does not offer treatment All results of examinations are mailed to the physician to whom the case is referred No charge is made for the service

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Dr Daniel J Glomset, F A C P, Des Moines, Dr George H Coleman, F A C P, Chicago, and Dr Grant H Laing, F A C P, Chicago, are Vice President, Secretary and Treasurer, respectively, of the Chicago Institute of Medicine

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Dr Alvis Greer, F A C P, Houston has been appointed Editor-in-Chief of the *Medical Record and Annals*

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Colonel G G Duncan, (MC), AUS, F A C P formerly Chief of Medical Service at the England General Hospital, Atlantic City, N J, is now assigned as Consultant in Medicine, Headquarters, Second Service Command, Governor's Island N Y

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Lt Col F R Dieuaide, F A C P, Chief of the Tropical Disease Treatment Branch, Office of the Surgeon General who recently returned from a three months' visit in three Pacific Theaters reported a small epidemic of skin diphtheria in the New Hebrides, which was brought under early control

It is thought the epidemic arose from carriers, the bacilli usually being carried in arm or leg wounds from which the organisms could be transferred readily to skin lesions in other persons or to the throats of susceptible soldiers

Individuals afflicted with this rare disease usually do not show serious effects, said Colonel Dieuaide although neuritis sometimes develops and there are occasional heart disturbances The symptoms generally disappear if the patient is put to rest the lesions properly cleaned and a sterile wet dressing applied Penicillin has been used but it is not necessary, he said, unless other bacteria are present "A case"

dose of antitoxin is enough to protect most patients from any serious consequence to themselves

The great importance of skin diphtheria, Colonel Dieuaide explained, lies in the danger that it may cause epidemics of ordinary diphtheria in soldiers, 45 to 50 per cent of whom are susceptible. The Medical Department has therefore taken prompt and effective steps to control the spread of the milder disease

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Major John R S Mays, (MC), AUS, (Associate), Baltimore, Md, has been appointed Consultant in Neuropsychiatry for the Burma Theater of Operations. Prior to his overseas assignment, Major Mays was Chief of the Neuropsychiatric Section at McGuire General Hospital, Richmond

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Dr Bernard E McGovern, F A C P, presented a paper before the San Fernando Valley Branch of the Los Angeles County Medical Association, Burbank, Calif, entitled, "The Diagnosis and Differential Diagnosis of Pulmonary Tuberculosis"

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#### MEDICAL DEPARTMENT TRAINS MEDICAL ADMINISTRATIVE CORPS OFFICERS AS BATTALION SURGEON ASSISTANTS

In order to relieve the critical shortage of doctors, the Medical Department has recently increased its quota for admission to officer candidate schools and has initiated a new program of training graduate administrative officers as battalion surgeon assistants. Between now and April 1945 appointments will be made in the Medical Administrative Corps after seventeen weeks training at Camp Berkeley, Texas and Carlisle Barracks, Pennsylvania

From among these graduates, officers with appropriate backgrounds will be selected to receive six weeks additional training at Camp Berkeley for duty assisting battalion surgeons. The special training consists principally of advanced first aid which will qualify these officers to relieve battalion surgeons of details and thus permit the surgeons time for purely medical and surgical work

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#### GENERAL MORGAN VISITS HOSPITALS

Brigadier General Hugh J Morgan, F A C P, Chief Consultant in Medicine, Office of The Surgeon General, recently returned from visiting Woodrow Wilson General Hospital, Staunton, Va, McGuire General Hospital, Richmond, Va, and Lawson General Hospital, Atlanta, Ga. He also attended the annual meeting of the Kentucky State Medical Association on September 19 in Lexington, Ky, where he participated in a symposium on new methods of administering penicillin

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#### INCIDENCE OF POLIOMYELITIS AMONG U S TROOPS

In the two-week period ending September 2, 1944, 20 cases of poliomyelitis were reported by Army installations in the United States. This represents a slightly higher incidence than for the corresponding period last year. The total incidence since the first of the year is somewhat lower than in the corresponding 8-month period of 1943. Although most of the cases have occurred in the states which have a high civilian incidence of the disease they have been widely scattered

Dr. Caleb O. Terrell, F A C P, Fort Worth, has been made a member of the Board of Regents of the University of Texas

### A C P POSTGRADUATE COURSES, SPRING, 1945

Below appears the full and detailed outline of Course No 1, CARDIOLOGY and Course No 2, MECHANICS OF DISEASE. The detailed outlines of other courses have not yet been completed by the Directors, and, therefore, are not ready for publication at this date (January 17, 1945)

Refer to a full page announcement of the Schedule of Courses in the advertising section in the back of this issue

THE PROGRAM OF POSTGRADUATE COURSES OF THE AMERICAN COLLEGE OF PHYSICIANS HAS BEEN APPROVED BY THE OFFICE OF DEFENSE TRANSPORTATION

#### COURSE No 1—CARDIOLOGY

(March 19-24, 1945)

COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY

630 West 168th Street

New York, New York

ROBERT L. LEVY, M D, F A C P, *Director*

(Maximal Registration, 50)

#### OFFICERS OF INSTRUCTION

Dana W. Atchley, M D, Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University, Associate Visiting Physician, Presbyterian Hospital

George Baehr, M D, F A C P, Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University, Director of Clinical Research, Mt Sinai Hospital

Alvan L. Barach, M D, F A C P, Associate Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University, Assistant Attending Physician, Presbyterian Hospital

Lois C. Collins, M D, Associate in Radiology, College of Physicians and Surgeons, Columbia University, Assistant Radiologist, Presbyterian Hospital

Arthur C. DeGraff, M D, F A C P, Samuel A. Brown Professor of Therapeutics, New York University College of Medicine, Visiting Physician, Bellevue Hospital

Clarence E. de la Chapelle, M D, F A C P, Professor of Clinical Medicine, New York University College of Medicine, Visiting Physician, Bellevue Hospital

William Dock, M D, Professor of Medicine, Long Island College of Medicine, Chief of Medical Service, The Long Island College Hospital, Brooklyn

A. Wilbur Duryee, M D, F A C P, Associate Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University, Attending Physician, New York Post-Graduate Hospital of Columbia University

Harry Gold, M D, Associate Professor of Pharmacology, Cornell University Medical College, Attending Cardiologist, Beth Israel Hospital

Ross Golden, M D, Professor of Radiology, College of Physicians and Surgeons, Columbia University, Director of Radiology, Presbyterian Hospital



- William Goldring, M D, F A C P, Associate Professor of Medicine, New York University College of Medicine, Associate Visiting Physician, Bellevue Hospital
- Magnus I Gregersen, M D, Professor of Physiology, College of Physicians and Surgeons, Columbia University
- Franklin M Hanger, Jr, M D, F A C P, Associate Professor of Medicine, College of Physicians and Surgeons, Columbia University, Associate Attending Physician, Presbyterian Hospital
- George H Humphreys, II, M D, F A C S, Assistant Professor of Clinical Surgery, College of Physicians and Surgeons, Columbia University, Assistant Attending Surgeon, Presbyterian Hospital
- Thomas H Hunter, M D, Resident Physician, Presbyterian Hospital
- Paul Klemperer, M D, Clinical Professor of Pathology, College of Physicians and Surgeons, Columbia University, Pathologist, Mt Sinai Hospital
- Robert L Levy, M D, F A C P, Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University, Associate Visiting Physician and Director of Department of Cardiology, Presbyterian Hospital
- Edwin P Maynard, Jr, M D, F A C P, Professor of Clinical Medicine, Long Island College of Medicine, Chief Attending Physician, The Brooklyn Hospital
- B S Oppenheimer, M D, F A C P, Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University, Consulting Physician, Mt Sinai Hospital
- Walter W Palmer, M D, F A C P, Baird Professor of Medicine, College of Physicians and Surgeons, Columbia University, Director of Medical Service, Presbyterian Hospital
- Harold E B Pardee, M D, F A C P, Assistant Professor of Clinical Medicine, Cornell University Medical College, Associate Attending Physician, New York Hospital
- Bronson S Ray, M D, Associate Professor of Surgery, Cornell University Medical College, Attending Surgeon, New York Hospital
- Dickinson W Richards, Jr, M D, Associate Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University, Visiting Physician, Bellevue Hospital
- David D Rutstein, M D, Instructor in Medicine, College of Physicians and Surgeons, Columbia University, Associate Visiting Physician, Bellevue Hospital, Deputy Commissioner of Health, New York City
- Edith E Sproul, M D, Assistant Professor of Pathology, College of Physicians and Surgeons, Columbia University
- Harold J Stewart, M D, F A C P, Associate Professor of Medicine, Cornell University Medical College, Attending Physician, New York Hospital
- Marcy L Sussman, M D, Assistant Professor of Radiology, College of Physicians and Surgeons, Columbia University, Radiologist, Mt Sinai Hospital
- William C Von Glahn, M D, Professor of Pathology, New York University College of Medicine, Director of Pathology, Bellevue Hospital
- Harold G Wolff, M D, F A C P, Associate Professor of Medicine, Cornell University Medical College, Attending Physician, New York Hospital

This course is designed to give, in one week, a summary of current knowledge concerning the more important aspects of cardiovascular diseases. The speakers have been chosen because of their special interest and scientific activity in the subjects they will discuss. Clinical features will be stressed throughout, but, in addition to diagnosis and treatment, basic physiologic and pathologic mechanisms will be considered.

All sessions will be held in amphitheatres at the College of Physicians and Surgeons, Columbia University.

Luncheon may be obtained at a reasonable price at Bard Hall, which is the student dormitory, located at 50 Haven Avenue. This is within three minutes' walking distance of the College. The lunch hour will be from 1 00 to 2 00 p m every day except Friday, March 23, when it will be from 12 00 noon to 1 00 p m.

### OUTLINE OF COURSE

#### Monday, March 19

##### A M Session—Amphitheatre A

- 9 00-10 00 Introductory Remarks  
Dr Palmer  
The Special Field of Cardiology  
Dr Levy
- 10 00-11 00 Blood Volume in Shock  
Dr Gregersen
- 11 00-12 00 Congenital Heart Disease  
Dr de la Chapelle
- 12 00- 1 00 Cardiovascular Syphilis  
Dr Maynard

##### P M Session—Amphitheatre A

- 2 00- 3 00 Public Health Aspects of Heart Disease with Special Reference to Rheumatic Fever  
Dr Rutstein
- 3 00- 4 00 Recent Studies of Peripheral Circulatory Failure  
Dr Richards
- 4 00- 5 00 The Electrocardiogram in Diagnosis and Prognosis  
Dr. Pardee

#### Tuesday, March 20

##### A M Session—Amphitheatre A

- 9 00-10 00 Therapeutic Use of Digitalis and Quinidine in Disorders of the Heart  
Dr Gold
- 10 00-11 00 Analysis and Diagnosis of Heart Disease by Use of Catheterization of Right Heart  
Dr Richards
- 11 00-12 00 Diuretics in the Treatment of Heart Failure  
Dr DeGraff
- 12 00- 1 00 Roentgenologic Diagnosis of Cardiovascular Diseases  
Dr Golden Dr Sussman and Dr Collins

##### P M Session—Amphitheatre A

- 2 00- 3 00 The Role of the Kidney in the Genesis of Hypertension  
Dr Goldring
- 3 00- 4 00 Coronary Heart Disease and Cardiac Pain  
Dr Levy
- 4 00- 5 00 Management of Patients with Heart Disease during Pregnancy and Labor  
Dr Pardee

#### Wednesday March 21

##### A M Session—Amphitheatre H

- 9 00-10 00 Use of Sedatives in Cardiac Disorders  
Dr DeGraff

- 10 00-11 00 Cardiac Arrhythmias  
Dr Stewart
- 11 00-12 00 Rheumatic Fever and Rheumatic Heart Disease  
Dr Hanger
- 12 00- 1 00 Roentgenologic Diagnosis of Cardiovascular Diseases  
Dr Golden, Dr Sussman and Dr Collins
- P M Session—Amphitheatre A
- 2 00- 3 15 Management of the Patient with Coronary Heart Disease  
Dr Levy
- 3 15- 5 00 Evaluation of Surgical Procedures in Cardiovascular Diseases  
Hypertension, Cardiac Pain and the Carotid Sinus Syndrome  
Dr Ray

Thursday, March 22

- A M Session—Amphitheatre F
- 9 00-10 00 Management of Occlusive Peripheral Vascular Disease  
Dr Duiyee
- 10 00-11 00 Treatment of Hypertensive Vascular Disease  
Dr Atchley
- 11 00-12 00 Cardiac Arrhythmias  
Dr Stewart
- 12 00- 1 00 Clinical Pathological Conference on Lupus Erythematosus and  
Periarteritis Nodosa  
Dr Baehi and Dr Klemperer
- P M Session—Amphitheatre F
- 2 00- 3 00 Pathology of Rheumatic Fever and Cardiovascular Syphilis  
Dr Von Glahn
- 3 00- 4 00 Inhalation of High Concentrations of Oxygen in Coronary Sclerosis  
and Congestive Heart Failure  
Dr Barach
- 4 00- 5 00 Clinical-Pathological Conference  
Dr Sproul

Friday, March 23

- A M Session—Amphitheatre F
- 9 00-10 00 Pathologic Anatomy of Arteriosclerosis and Coronary Heart  
Disease  
Dr Klempeier
- 10 00-11 00 Treatment of Bacterial Endocarditis with Penicillin, Heparin and  
the Sulfonamides  
Dr Hunter
- 11 00-12 00 Treatment and Prophylaxis of Rheumatic Fever  
Dr Hanger
- P M Session—Amphitheatre II
- 1 00- 2 00 Diagnosis, Medical Management and Surgical Treatment of  
Chronic Constrictive Pericarditis  
Dr Stewart
- 2 00- 3 00 Cardiac Disorders in Thyroid Dysfunction  
Dr de la Chapelle
- 3 00- 4 00 Surgical Treatment of Patent Ductus Arteriosus  
Dr Humphreys
- 4 00- 5 00 Neurocirculatory Asthema and Related Problems  
Dr Oppenheimer

Saturday, March 24

A M Session—Amphitheatre H

9 00-10 00 Rest in the Treatment of Cardiac Conditions  
Dr Dock

10 00-11 00 Psychosomatic Aspects of Cardiovascular Diseases  
Dr Wolff

11 00- 1 00 Medical Clinic  
Dr Palmer and Associates

# COURSE No 2—MECHANICS OF DISEASE

(April 9-21, 1945)

PETER BENT BRIGHAM HOSPITAL AND HARVARD MEDICAL SCHOOL  
Boston, Mass

GEORGE W THORN, M D, F A C P, *Director*

(Minimal Registration, 20, Maximal Registration, 35)

## OFFICERS OF INSTRUCTION

Fuller Albright, M D Physician, Massachusetts General Hospital, Associate Professor of Medicine Harvard Medical School

S Howard Armstrong Jr, M D, Associate in Medicine, Peter Bent Brigham Hospital, Instructor in Medicine and Research Associate in Physical Chemistry Harvard Medical School

Edwin B Astwood M D Associate in Medicine, Peter Bent Brigham Hospital Assistant Professor of Pharmacotherapy, Harvard Medical School

Donald L Augustine, S D Associate Professor of Comparative Pathology and Tropical Medicine, Harvard Medical School

C Cabell Bailey, M D, Physician, New England Deaconess Hospital, Research Fellow in Medicine Harvard Medical School

Orville T Bailey M D, Associate in Pathology, Harvard Medical School

C Sidney Burwell M D F A C P Physician, Peter Bent Brigham Hospital Research Professor of Clinical Medicine and Dean, Harvard Medical School

William B Castle, M D, F A C P, Associate Director of the Thorndike Memorial Laboratory and Director of the Second and Fourth Medical Services Boston City Hospital Professor of Medicine, Harvard Medical School

Edwin J Cohn, Ph D Professor of Biological Chemistry, Harvard Medical School

Charles S Davidson M D Assistant Director of the Second and Fourth Medical Services, Boston City Hospital, Assistant in Medicine Harvard Medical School

Frank C d'Elsaux M D Associate in Psychiatry, Peter Bent Brigham Hospital, Instructor in Psychiatry Harvard Medical School

Derek E Denny-Brown, M D F R C P, Director of the Neurological Unit, Boston City Hospital Professor of Neurology Harvard Medical School

Lewis Dexter, M D, Associate in Medicine Peter Bent Brigham Hospital, Associate in Medicine, Harvard Medical School

Louis K Diamond M D Visiting Physician Children's Hospital, Assistant Professor of Pediatrics, Harvard Medical School

E Stanley Emery, M D, Senior Associate in Medicine, Peter Bent Brigham Hospital Instructor in Medicine Harvard Medical School

John F Enders Ph D Associate Professor of Bacteriology and Immunology Harvard Medical School

- Sidney Farber, M D , Pathologist, Children's Hospital, Assistant Professor of Pathology, Harvard Medical School
- Cutting B Favour, M D , Junior Associate in Medicine, Peter Bent Brigham Hospital, Assistant in Medicine, Harvard Medical School
- Clement A Finch, M D , Junior Associate in Medicine, Peter Bent Brigham Hospital, Assistant in Medicine, Harvard Medical School
- Quentin M Geiman, Ph D , Assistant Professor of Tropical Diseases, Harvard Medical School
- Robert E Gross, M D , F A C S , Associate in Surgery, Peter Bent Brigham Hospital, Associate Visiting Surgeon, Children's Hospital, Assistant Professor of Surgery, Harvard Medical School
- D Mark Hegsted, Ph D , Associate in Nutrition, Harvard Medical School
- John Homans, M D , Acting Surgeon in Charge of Circulatory Diseases, Peter Bent Brigham Hospital, Clinical Professor of Surgery, Emeritus, Harvard Medical School
- Clinton v Z Hawn, M D , Instructor in Pathology, Harvard Medical School
- Henry Jackson, Jr, M D , Assistant Visiting Physician, Boston City Hospital, Assistant Professor of Medicine, Harvard Medical School
- Charles A Janeway, M D , Senior Associate in Medicine, Peter Bent Brigham Hospital, Visiting Physician, Children's Hospital, Assistant Professor of Pediatrics and Instructor in Bacteriology and Immunology, Harvard Medical School
- Chester M Jones, M D , F A C P , Physician, Massachusetts General Hospital, Clinical Professor of Medicine, Harvard Medical School
- Elliott P Joslin, M D , F A C P , Physician, New England Deaconess Hospital, Medical Director, George F Baker Clinic, Clinical Professor of Medicine, Emeritus, Harvard Medical School
- Thomas D Kinney, M D , Associate Pathologist, Peter Bent Brigham Hospital, Instructor in Pathology, Harvard Medical School
- Otto Kraye, M D , Consulting Pharmacologist, Peter Bent Brigham Hospital, Associate Professor of Comparative Pharmacology and Head of the Department, Harvard Medical School
- Eugene M Landis, M D , F A C P , Consulting Physiologist, Peter Bent Brigham Hospital, George Higginson Professor of Physiology, Harvard Medical School
- Samuel A Levine, M D , F A C P , Physician, Peter Bent Brigham Hospital, Assistant Professor of Medicine, Harvard Medical School
- Arthur J Lockhart, M D , Assistant in Medicine, Peter Bent Brigham Hospital, Assistant in Medicine, Harvard Medical School
- F William Marlow, Jr, M D , Senior Associate in Medicine, Peter Bent Brigham Hospital, Associate in Medicine, Harvard Medical School
- John M McKibbin, Ph D , Instructor in Nutrition, Harvard Medical School
- James H Means, M D , F A C P , Chief of Medical Services, Massachusetts General Hospital, Jackson Professor of Clinical Medicine, Harvard Medical School
- George R Minot, M D , F A C P , Director of the Thorndike Memorial Laboratory, Boston City Hospital, Professor of Medicine, Harvard Medical School
- Robert T Monroe, M D , F A C P , Senior Associate in Medicine, Peter Bent Brigham Hospital, Associate in Medicine, Harvard Medical School
- William P Murphy, M D , Senior Associate in Medicine, Peter Bent Brigham Hospital, Associate in Medicine, Harvard Medical School
- Francis C Newton, M D , F A C S , Surgeon-in-Chief (Acting), Peter Bent Brigham Hospital, Assistant Professor of Surgery, Harvard Medical School
- Harlan I Newton, M D , F A C S , Senior Associate in Surgery, Peter Bent Brigham Hospital, Associate in Surgery, Harvard Medical School
- James P O'Hare, M D , Physician, Peter Bent Brigham Hospital, Assistant Professor of Medicine, Harvard Medical School

- William C Quinby, M D, F A C S, Urological Surgeon, Peter Bent Brigham Hospital, Clinical Professor of Genito-Urinary Surgery, Emeritus, Harvard Medical School
- Rulon W Rawson, M D, Assistant in Medicine, Massachusetts General Hospital, Instructor and Henry P Walcott Fellow in Clinical Medicine, Harvard Medical School
- Howard F Root, M D, F A C P, Physician-in-Chief, New England Deaconess Hospital, Associate in Medicine, Harvard Medical School
- George C Shattuck, M D, Consultant in Tropical Medicine, Peter Bent Brigham Hospital, Clinical Professor of Tropical Medicine, Harvard Medical School
- Richard M Smith, M D, Physician-in-Chief, Children's Hospital, Thomas Morgan Rotch Professor of Pediatrics, Harvard Medical School
- Reginald H Smithwick, M D, F A C S, Associate Visiting Surgeon, Massachusetts General Hospital, Instructor in Surgery, Harvard Medical School
- Merrill C Sosman, M D, Roentgenologist, Peter Bent Brigham Hospital, Clinical Professor of Roentgenology, Harvard Medical School
- Frederick J Stare, M D, Associate in Medicine, Peter Bent Brigham Hospital, Associate Professor of Nutrition, Harvard Medical School
- Siegfried J Tanuhauser, M D, Associate Chief, Pratt Diagnostic Hospital, Professor of Clinical Medicine, Tufts College Medical School
- George W Thorn, M D, F A C P, Physician-in-Chief, Peter Bent Brigham Hospital, Hersey Professor of the Theory and Practice of Physic, Harvard Medical School
- Priscilla White, M D, F A C P, Physician, New England Deaconess Hospital, Instructor in Pediatrics, Tufts College Medical School
- S Burt Wolbach M D, Pathologist, Peter Bent Brigham Hospital, Shattuck Professor of Pathological Anatomy, Harvard Medical School

All meetings will be held in the Amphitheatre of the Peter Bent Brigham Hospital unless otherwise announced

This course is primarily designed for internists who not only wish to keep abreast of recent developments in the field of Internal Medicine, but who are actually interested in learning newer techniques in the diagnosis and treatment of disease. With this in mind, the group has been limited to a maximum of thirty-five so that adequate provision may be made for demonstrations and laboratory work

#### OUTLINE OF COURSE

##### Monday, April 9

###### A M Session

9 00-12 00 Pulmonary Embolism

Dr Dexter, Dr Homans, Dr Lockhart and Dr Sosman

12 00- 1 00 Clinical-Pathological Conference

Dr Emery and Dr Wolbach

###### P M Session

2 00- 4 00 Bacteriological Techniques Demonstrations and Laboratory

Dr Favour and Dr Janeway

4 00- 5 00 Neurological Rounds

Dr Denny-Brown

##### Tuesday, April 10

###### A M Session

9 00-12 00 Adrenal Disorders

Dr Albright and Dr Thorn

12 00- 1 00 X-ray Conference  
Dr Sosman

P M Session

2 00- 5 00 Blood Proteins

Dr Armstrong, Dr Cohn and Dr Janeway, with a visit to the  
Plasma Fractionation Laboratory

Evening

8 15-10 00 Harvard Medical Society

Wednesday, April 11

A M Session

9 00-12 00 Nutrition

Dr Hegsted, Dr Stare, Dr Thorn and Associates

12 00- 1 00 Clinical-Pathological Conference, Children's Hospital  
Dr Farber and Dr Smith

P M Session

2 00- 5 00 Diseases of the Liver

Dr Armstrong, Dr Jones, Dr McKibben, Dr Sosman, Dr  
Stare and Dr Thorn

Thursday, April 12

A M Session

9 00- 1 00 Sulfonamide and Penicillin Therapy, Demonstrations  
Dr Favour, Dr Janeway and Dr Marlow

P M Session

2 00- 5 00 Diseases of the Kidney

Dr Dexter, Dr O'Hare, Dr Sosman and Dr Thorn

Friday, April 13

A M Session

9 00- 1 00 Thyroid Disorders

Dr Astwood, Dr Levine, Dr Means, Dr Rawson and Dr  
Thorn

P M Session

2 00- 4 00 Peripheral Vascular Disease, Demonstrations and Laboratory

Dr Landis and Associates, Department of Physiology

4 00- 6 00 Problems in Psychosomatic Medicine

Dr d'Elseaux

Saturday, April 14

A M Session

9 00-10 00 Problems in Geriatrics

Dr Monroe

10 00-12 00 Medical Grand Rounds

Monday, April 16

A M Session

9 00-12 00 Cardiac Arrhythmias

Dr Burwell, Dr Dexter and Dr Levine

12 00- 1 00 Clinical-Pathological Conference

Dr Thannhauser and Dr Wolbach,

## P M Session

- 2 00- 4 00 Congenital Heart Disease  
                   Dr Burwell, Dr Levine and Dr Gross
- 4 00- 5 00 Neurological Rounds  
                   Dr Denny-Brown

## Tuesday, April 17

## A M Session

- 9 00-12 00 Pulmonary Diseases  
                   Dr Burwell, Dr Favour and Dr Newton
- 12 00- 1 00 X-ray Conference  
                   Dr Sosman

## P M Session

- 2 00- 5 00 Hypertension  
                   Dr Dexter, Dr Krayner, Dr O'Hare and Dr Smithwick

## Wednesday, April 18

## A M Session

- 9 00-12 00 Virus Diseases  
                   Dr Enders, Dr Favour and Dr Janeway
- 12 00- 1 00 Clinical-Pathological Conference Children's Hospital  
                   Dr Farber and Dr Smith

## P M Session

- 2 00- 5 00 Tropical Diseases, Demonstrations and Laboratory  
                   Dr Augustine, Dr Geiman and Dr Shattuck, Department of  
                   Tropical Medicine

## Evening

- 8 00-10 00 Boston Society of Biologists

## Thursday, April 19

## A M Session

- 9 00- 1 00 Hematology, Demonstrations and Laboratory Technique  
                   Dr Diamond, Dr Finch and Dr Murphy

## P M Session

- 2 00- 4 00 Erythema Nodosum, Lupus Erythematosus, Polyarteritis  
                   Dr Armstrong, Dr Favour, Dr Hawn and Dr Sosman
- 4 00- 6 00 Problems in Psychosomatic Medicine  
                   Dr d Elseaux

## Friday, April 20

## A M Session

- 9 00- 1 00 Diabetes Mellitus  
                   Dr C C Bailey, Dr O T Bailey, Dr Jo-lin, Dr Root  
                   Dr Thorn and Dr White

## P M Session

- 2 00- 5 00 Disorders of the Blood  
                   Dr Castle, Dr Davidson, Dr Jackson and Dr Minor

## Saturday April 21

## A M Session

- 9 00-10 00 Gout  
                   Dr Thorn
- 10 00-12 00 Medical Grand Rounds



## WAR-TIME GRADUATE MEDICAL MEETINGS

REGION No 1 (Maine, New Hampshire, Vermont, Massachusetts) and REGION No 2 (Connecticut, Rhode Island—New England Committee for War-Time Graduate Medical Meetings—Dr W R Ohler, Chairman, Dr L E Parkins, Secretary, Dr S B Weld, Dr A M Burgess, Dr C S Keefer, Dr F T Hill, Dr J P Bowler, Dr B F Cook, Executive Committee members

*Station Hospital, Dow Field, Bangor, Maine*

March 20 The Skin

*Dispensary, U S Naval Air Station, Brunswick, Maine*

March 15 Head, Spine and Nerve Injuries

*Station Hospital, Fort Williams, Portland, Maine*

March 15 Tropical Diseases, to Include Malaria and Other Insect-Borne Diseases

*Station Hospital, Presque Isle, Maine*

March 15 Contagious Diseases and Complications

*Station Hospital, Greiner Field, Manchester, New Hampshire*

March 14 Pilonidal Sinus and Common Diseases of the Anus and Rectum

*U S Naval Hospital, Portsmouth, New Hampshire*

March 15 Cardiac Neuroses, Cardiac Emergencies, Cardiac Rehabilitation

*Boston Area Station Hospital, Waltham, Massachusetts*

March 15 Burns and Reconstruction Surgery

*U S Naval Hospital, Chelsea, Massachusetts*

March 15 The Use of Penicillin and the Sulfa Drugs

*Lovell General Hospital, Fort Devens, Massachusetts*

March 15 Diarrheal Diseases

*Station Hospital, Camp Edwards, Massachusetts*

March 15 Stomach, Biliary Tract, Intestinal Disorders

*Cushing General Hospital, Frammingham, Massachusetts*

March 15 Chest and Abdominal Injuries

*Station Hospital, Camp Myles Standish, Taunton, Massachusetts*

March 15 The Psychoneuroses and Their Management

*U S Marine Hospital, Brighton, Massachusetts*

March 15 The Pneumonias and Other Respiratory Infections

*Station Hospital, Westover Field, Chicopee Falls, Massachusetts or U S Naval Convalescent Hospital, Springfield, Massachusetts*

March 15 Cardiac Neuroses, Cardiac Emergencies, Cardiac Rehabilitation

*Dispensary, U S Naval Construction Training Center, Davisville, Rhode Island*

March 15 Fractures of Extremities

*U S Naval Hospital, Newport, Rhode Island*

March 15 Joint Injuries

*Station Hospital, Bradley Field, Windsor Locks, Connecticut*

March 15 The Pneumonias and Other Respiratory Infections

*Station Hospital, Fort H G Wright, Fishers Island, New York*

March 15 Acute Infections of the Central Nervous System.

REGION No 3 (New York)—Dr O R Jones, Chairman, Dr N Jolliffe, Dr H W Cave

*Induction Center, Grand Central Palace, New York, New York*

February 16 Head Injuries—Dr Eli Jefferson Browder

REGION No 4 (Eastern Pennsylvania, Delaware, New Jersey)—Dr B P Widmann  
Chairman, Dr J S Rodman, Dr S P Reimann

*U S Naval Hospital, Philadelphia, Pennsylvania*

February 23 The Esophagus and Its Diseases—Dr L H Clerf

March 23 Surgical Technic in Acute Appendicitis—Dr George Muller

REGION No 5 (Maryland, District of Columbia, Virginia, West Virginia)—Dr I A  
Lyon, Chairman, Dr C R Edwards, Dr C B Conklin

*Newton D Baker General Hospital, Martinsburg, West Virginia*

February 19 Treatment of Patients with Paraplegia Due to War Injuries—Dr  
Donald Munro

Liver Diseases Seen in the Present War—Dr Wallace Yater

March 5 Diagnosis and Treatment of Cardiovascular Conditions Peculiar to Military  
Life—Dr Louis Hamman

Penetrating Wounds of the Abdomen

March 19 Experiences with Malaria—Colonel Paul F Russell

Diagnosis of Diarrheal Diseases—Lieutenant Colonel Hardy Kemp

*Station Hospital, Fort Belvoir, Virginia*

February 26 Skin Eruptions of the Eczema Group—Dr Walter O Teichmann

March 12 General Principles of Plastic Surgery—Dr Robert E Moran

March 26 Seasonal Hay Fever—Dr Grafton Tyler Brown

*A A F Regional Hospital, Langley Field, Virginia*

February 23 Internal Medicine

Neurology and Neurosurgery

March 30 Psychiatry—Dr R Finley Gayle

Orthopedic Surgery

REGION No 8 (Western Pennsylvania, Ohio)—Dr C A Doan Chairman, Dr P G  
Smith Dr F M Douglass

*Circle General Hospital, Cleveland, Ohio*

February 27 Technic of Closure of Colostomies—Dr Thomas E Jones

March 27 Problems in the Diagnosis and Management of Coronary Artery Disease  
—Dr R W Scott

*Air Base Hospital, Patterson Field, Dayton, Ohio*

February 21 Diagnosis and Surgical Treatment of Acute Cholecystitis—Dr George  
Hener

REGION No 14 (Indiana, Illinois, Wisconsin)—Dr W O Thompson Chairman, Dr  
N C Gilbert, Dr W H Cole Dr W D Gatch, Dr R M Moore Dr H M  
Baker, Dr E R Schmidt, Dr E L Sevringhaus Dr F D Murphy

*Station Hospital, Truax Field, Wisconsin*

February 28 Heart Disease—Dr Chester M Kurtz

March 14 Arthritis—Dr Milton C Bornman

March 28 Peripheral Vascular Diseases—Dr Geza de Lathas

*Gardner General Hospital, Chicago, Illinois*

February 21 Present Status of Medical Planning—Dr Morris Finckel

February 28 Plexus and Peripheral Nerve Injuries

March 7 Relationship between Deficiency Diseases and the Gastrointestinal Tract  
—Dr Clifford Barborka

March 14 Dermatological Diseases

March 23 Sequelae of Head Injuries—Dr Paul Bucy

March 28 Burns and Plastic Surgery

*Station Hospital, Fort Sheridan, Illinois*

February 28 Burns and Plastic Surgery

March 14 Malignancies in the Army Age Group—Medical X-ray and Surgical Diagnosis and Treatment

March 28 Endocrinology

*Mayo General Hospital, Galesburg, Illinois*

February 28 Endocrinology

March 14 Virus and Rickettsial Diseases—Medical and Neurological Diseases and Treatment

March 28 Psychosomatic Medicine

*Vaughan General Hospital, Illinois*

February 28 Psychosomatic Medicine

March 14 Wound Healing and Tendon Surgery

March 28 Mental Hygiene and the Prevention of Neuroses in War

*Station Hospital, Camp Ellis, Illinois*

February 28 Mental Hygiene and the Prevention of Neuroses in War

March 14 Thrombosis, Thrombophlebitis and Anticoagulants in Less Common Peripheral Vascular Diseases

March 28 Peptic Ulcer, Gall Bladder and Liver Diseases

*Station Hospital, Chaute Field, Illinois*

February 28 Diseases of the Kidneys—Urogenital Tract

March 14 Laboratory Diagnosis and Its Relationship to Medical and Surgical Treatment

March 28 High Blood Pressure

*Billings General Hospital, Fort Benjamin Harrison, Indiana*

February 28 High Blood Pressure

March 14 Brain and Spinal Cord Injuries

March 28 Conditions Affecting Glucose Metabolism

*Wakeman General Hospital, Camp Atterbury, Indiana*

February 28 Conditions Affecting Glucose Metabolism

March 14 Plexus and Peripheral Nerve Injuries

March 28 Diseases of the Intestinal Tract—Medical and Surgical Diagnosis and Care

REGION No 16 (Missouri, Kansas, Arkansas, Oklahoma)—Dr F D Dickson, Chairman, Dr O P J Falk, Dr H H Turner

*Station Hospital, Roscreans Field, St Joseph, Missouri*

March 15 General Surgery

Venereal Diseases and Urology

*Regional Hospital, Fort Riley, Kansas*

March 15 General Surgery

Shock, Burns and Blood Derivatives

March 29 Chest Surgery

Diseases of the Blood

*Winter General Hospital, Topeka, Kansas*

February 22 Plastic and Maxillary Surgery—Dr Earl C Padgett  
Clinical Psychiatry—Dr G Leonard Harrington

## SPECIAL NOTICES

ANNOUNCEMENT OF THE SPRING REFRESHER COURSE IN OTOLARYNGOLOGY BY THE  
UNIVERSITY OF ILLINOIS COLLEGE OF MEDICINE

The 5th semi-annual refresher course in laryngology, rhinology and otology will be conducted by the University of Illinois, College of Medicine at the College in Chicago, March 26 to 31 inclusive, 1945. Although the course will be largely didactic, some clinical instruction will be included. This course is intended primarily for ear, nose and throat specialists. As the registration is limited to thirty, applications will be considered in the order in which they are received. The fee is \$50.00. When writing for application please give details concerning school and year of graduation, and past training and experience.

*Address*—Dr. A. R. Hollender, Chairman, Refresher Course Committee, Department of Otolaryngology, University of Illinois, College of Medicine, 1853 West Polk Street, Chicago 12, Illinois.

*OBITUARY*

## DR. FREDERICK GEORGE SPEIDEL

Dr. Frederick George Speidel, F A C P, Louisville, Kentucky, died suddenly of heart disease on October 15, 1944.

Dr. Speidel was born on March 14, 1889. He received his Medical Degree in 1917 from the University of Louisville School of Medicine, and in his later career pursued postgraduate study at the U. S. Naval Medical School, Rockefeller Institute for Medical Research, and the University of Michigan. During World War I and immediately thereafter he served for a time as instructor in Clinical Chemistry at the U. S. Naval Medical School. Thereafter he was Assistant in Medicine (1919-1922), instructor in Therapeutics (1922-1923), clinical instructor in Pharmacology (1923-1935), and assistant clinical professor of Pharmacology (since 1935) at his alma mater. For many years he was a member of the staff of the Kentucky Baptist, St. Anthony's, and Kosair Crippled Children's Hospitals and the Norton Memorial Infirmary.

Dr. Speidel had served as Secretary-Treasurer, First and Second Vice-Presidents of the Jefferson County Medical Society, and also as Secretary-Treasurer and President of the Society of Physicians and Surgeons. He was a member of the Kentucky State Medical Association and the Southern Medical Association, a Fellow of the American Medical Association, and had been a Fellow of the American College of Physicians since 1938. He was a diplomate of the American Board of Internal Medicine, and the author of numerous published papers.

Dr. Speidel was one of the outstanding internists of Louisville, and was extremely popular with his patients and with the entire medical profession. He felt with so many physicians absent from the community that he could carry on in spite of everything, and it is generally believed by his friends that this added strain was responsible for his very sudden death from coronary thrombosis.

C. W. DOWDEN, M. D., F. A. C. P.,  
Governor for Kentucky

# ABSTRACTED AND ABRIDGED MINUTES

## BOARD OF REGENTS

PHILADELPHIA, DECEMBER 16, 1944

The regular autumn meeting of the Board of Regents of the American College of Physicians was held at the College Headquarters, Philadelphia, December 16, 1944, with President Ernest E. Irons presiding. Fifteen members of the Board were in attendance.

The Executive Secretary read abstracted minutes of the preceding meeting of the Board and presented numerous communications, none of which required special action other than the following:

1. A resolution was adopted, discouraging a recently organized medical society from scheduling its meetings at the same time and with the meeting of the American College of Physicians.
2. It was unanimously voted to continue the Conference Committee on Graduate Training in Medicine to confer and work with a similar Committee from the American Board of Internal Medicine and the Council on Medical Education and Hospitals of the American Medical Association. The following appointments were made by President Irons to serve on this Committee:

Dr. Reginald Fitz, Boston  
Dr. LeRoy Sloan, Chicago

The Secretary General, Dr. George Morris Piersol, read a list of the deaths of 47 Fellows and 5 Associates since the preceding meeting of the Board. Included within the list were the names of Dr. Charles Hartwell Cocke, Asheville, N. C., First Vice President of the College, and Dr. William B. Breed, Boston, Mass., Chairman of the Board of Governors. At the request of the Chairman the Board arose and stood in silence in respect to those deceased.

Dr. Piersol then reported for record in the minutes, the names of 24 additional Life Members who had subscribed to the Endowment Fund of the College since the preceding meeting of the Board of Regents.

As Chairman of the Committee on Credentials, Dr. Piersol proceeded with the report of that Committee. "I would like to remind the Regents that the Credentials Committee, in the past few months, has suffered serious catastrophes in the deaths of Dr. Charles Hartwell Cocke and Dr. William B. Breed, who died within a short time of each other, leaving two vacancies on this Committee of six. Particularly do I want to mention these men and to pay a tribute to them personally for the long years of arduous and enthusiastic work which they performed. The Committee deeply regrets the loss of these active and efficient men."

"The Credentials Committee met yesterday and reviewed a large number of candidates. An analysis of the recommendations of the Committee is as follows:

A. Candidates for Fellowship	
Recommended for advancement from Associate-ship	105
Recommended for direct election	23 128

Recommended for election first for Associateship	16
Deferred	32
Rejected	18

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Total number of candidates for Fellowship	194
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B Candidates for Associateship	
Recommended for election	167
Deferred	33
Rejected	22

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Total number of candidates for Associateship	222"
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At this point, mimeographed lists of the candidates for Fellowship and Associateship were passed to each Regent for survey. Formal resolutions were adopted electing 128 candidates to Fellowship and 183 candidates to Associateship (these names were published in the News Notes section of the January, 1945, Issue of this journal).

On the recommendation of the Credentials Committee, the term of Associateship was extended beyond the customary five-year maximum for 26 Associates now on military service, the names of five Associates not on military service, who had failed to qualify for advancement to Fellowship within the five-year period, were dropped from the Roster.

An analysis of the group of candidates elected to Associateship on December 17, 1939, five years previous to this meeting, is as follows:

Advanced to Fellowship	114 (77 %)
Deceased	3
Dropped for failure to take up election	1
Dropped for failure to qualify for Fellowship	5
Associate term extended because of military service	26
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	149

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On recommendation of the Committee on Credentials, Dr. William R. Vis, Grand Rapids, Mich., was re-instated to active Fellowship in the College. On recommendation by the Committee on Credentials, the Board of Regents approved that areas, such as New York City, Brooklyn and other comparable communities may, on selection by the local Governor, have a consulting committee of five or six Fellows by whom all proposals will be reviewed before endorsement by the Governor, for recommendation to the Committee on Credentials.

Commenting on candidates presented for direct Fellowship in the College, Dr. Piersol said, "It is astonishing how many men without any adequate qualifications are being proposed for direct election to Fellowship. The Regents and Governors need to do some missionary work in this direction. The credentials of those the Committee recommended for direct Fellowship were scrutinized with unusual care, and those selected represent outstanding men in the field of internal medicine and have the necessary qualifications to justify their election. However, at least 16 of the candidates proposed for direct election were first recommended for election to Associateship and several other candidates for direct election were rejected."

"The Credentials Committee again has the temerity to recommend to the Board of Regents that certification be made a prerequisite for Associateship, rather than merely for advancement to Fellowship, and if approved, that the Committee shall be authorized to draw up proper wording for this change in the regulations. As you know, since April 6, 1940, advancement to Fellowship requires certification by the national board in any specialty where such a board exists. The Committee is

now seeking some further definite yardstick by which they can measure a man's professional ability. The Committee has felt for a long time that the present method is inadequate, uncertain and sometimes unjust. If this change in requirements is adopted, let the Associate term then be devoted to a demonstration of the candidate's competency, scientific attainments and other contributions. As a matter of fact, many of the present candidates for Associateship are already certified and many of them have the idea that certification is all that is necessary to become a Fellow, which, of course, is wrong. The present system is not entirely satisfactory, if candidates are required to be certified before becoming Associates, they will then realize that to become a Fellow they have to do something more, which should be a stimulus and should elevate Fellowship to a higher plane."

There was extended discussion of the matter among members of the Credentials Committee and the members of the Board of Regents and opinions were in some cases divergent. On motion by Dr Piersol, seconded by Dr Fitz, and regularly carried, it was resolved that this matter should be placed on the agenda at the next joint meeting of the Board of Regents and Board of Governors. During the discussion of this motion, it was revealed that at the present time, certification is a minimum professional requirement for advancement to Fellowship but that the Credentials Committee will not accept certification as the sole professional requirement for Fellowship, the Committee emphasizes the need of some productivity, such as publications, a thesis or other material, with definite consideration given to appointments, maturity, reputation and standing. A Fellow of the College must be something more than just a good doctor who is certified. He must be an internist or a specialist in an allied specialty, who is able to take part in the scientific aspects of his specialty and demonstrate his fitness and interest in that specialty. Fellowship must be looked upon as a definite and distinct honor, that stamps a man not only as a good internist, but as an outstanding one.

Dr James E Paullin, Chairman of the Committee on Constitution and By-laws reported that two matters had been submitted to the Committee for consideration for amendments to the By-laws

- 1 The By-laws should provide for the Board of Governors, similarly as it provides for the Board of Regents, some limitation for the term of office
- 2 A change in the method of appointing the Nominating Committee

After extensive discussion, the following resolutions were adopted

- 1 RESOLVED, that a proper By-law be prepared providing for the limitation in the term of office of members of the Board of Governors to two consecutive terms of three years each, and that this By-law be presented for adoption at the next annual business meeting in the spring of 1945
- 2 RESOLVED, that inasmuch as the present provision for the nomination and election of Officers, Regents and Governors is wholly democratic and has worked satisfactorily and well ever since the adoption of the present By-laws, no change shall be recommended

Dr Walter W Palmer, Chairman of the Committee on the ANNALS OF INTERNAL MEDICINE, presented a report for that Committee making the observation that the income from the journal is at present very largely responsible for much of the surplus of the College, because of large orders received from the Army and Navy for distribution to medical installations all over the world. The Regents gave approval for the Army Medical Library to reproduce material from the ANNALS for use during the



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war. A request from a publishing concern in Brazil for permission to translate the *ANNALS* into Portuguese, but to utilize the new publication in their country for their own advertising and aggrandizement, was refused.

Dr. Paul Clough, as Editor, reported primarily on the acquisition of material for publication in the *ANNALS* and the preparation of book reviews. There had been a definite, gradual falling off in the number of acceptable articles for publication in the *ANNALS*. Many speakers during the war have found inadequate time to prepare manuscripts, and frequently speak extemporaneously; such papers have not been available in many instances for publication. Dr. Clough reported that he had not been able to give much time personally to the matter of writing book reviews, and most of the reviewers who had done this for the *ANNALS* in the past, are now on active military duty. He suggested no remedy for the present shortage of reviews. On the recommendation of Dr. O. H. Perry Pepper, Chairman of the Finance Committee, an additional appropriation was made available to the Acting Editor to enable him to attend in person more of the regional meetings of the College in pursuit of suitable presentations for publication in the *ANNALS*. The opinion was expressed in discussion that the College has allowed possibly too much of the material that appears in the *ANNALS* to be derived from its meetings where it is unlikely, especially at the regional meetings, for new work to be announced for the first time. It would be a marked improvement if a greater effort might be made to obtain for the *ANNALS* more of the new papers covering new discoveries, new reports and new advances.

The Executive Secretary, Mr. Loveland, was called upon to make a report for the Committee on Educational Policy and the Advisory Committee on Postgraduate Courses.

MR. LOVELAND: All members of the Committee on Educational Policy are absent, and the Chairman of the Advisory Committee on Postgraduate Courses, Captain Bortz, is in the Pacific. Consequently, no meeting of this Committee could be held yesterday.

Your Executive Secretary has carried on this work, with consultation with the members of the Advisory Committee on Postgraduate Courses, and submits the following report:

I. Spring, 1944, Courses: (Total Registration, 407)

Course No. 1, *General Medicine*, University of Michigan, Dr. C. C. Sturgis, Director, (April 10-15).

Course No. 2, *Clinical Medicine with Special Emphasis upon the Hematologic Viewpoint*, Ohio State University, Dr. Charles A. Doan, Director, (April 17-22).

Course No. 3, *Internal Medicine*, Massachusetts General Hospital, Dr. James H. Means, Director, (April 24-29).

The above courses were reported upon by Captain Bortz at the Chicago meeting of this Board on April 1.

II. Autumn, 1944, Courses: (Total Registration, 447)

Course No. 1, *Cardiology*, Massachusetts General Hospital, Dr. Paul D. White, Director, (October 2-7).

Course No. 2, *General Medicine*, University of Oregon, Dr. Homer P. Rush, Director, (October 9-14).

Course No. 3, *Internal Medicine*, University of Minnesota, Drs. William A. O'Brien, Cecil J. Watson and E. H. Ryncarson, Directors, (October 9-14).

Course No. 4, *Allergy*, Roosevelt Hospital, New York City, Dr. Robert A. Cooke, Director, (October 16-21).

Course No. 5, *Internal Medicine*, Chicago Institutions, Dr. Willard O. Thompson, Director, (October 23-November 4).

Course No. 6, *Special Medicine*, Philadelphia Institutions, Dr. Thomas M. McMillan, Director, (December 4-15).

We were gratified at being able to successfully put on for the first time one of our courses on the West Coast. Dr. Rush, with his associates, including Dr. Coffen, did an exceedingly fine job. Those taking the courses were highly pleased and many letters of appreciation were received. We predict that now that we have successfully established a beginning on the West Coast, the demand for courses there will increase.

Dr. White's course in Cardiology, while intended to be limited to 50, grew to 71, and more than one hundred applicants had to be turned away. There was an urgent request for the repetition of this course this coming winter or spring, but Dr. White was so exhausted that he has asked to have the repetition of the course delayed at least until the autumn of 1945.

The course in Internal Medicine at the University of Minnesota was up to its usual standard, but the demand was not as great for the course this autumn as it had been on previous occasions. However, there was a very satisfactory registration, and those in attendance were highly pleased with the course.

Course No. 4, Allergy, by Dr. Cooke, which has been given several times previously, had the largest registration this year in its history. Dr. Cooke always puts on a fine course and is recognized the country over as one of our finest teachers in the field of Allergy.

Course No. 5 in Internal Medicine at Chicago Institutions was held in Thorne Hall, Northwestern University, and had the active interest and support of all our Officers and members in Chicago. The course was intended to be limited to 60, but the Director, Dr. Thompson, was enthusiastic about accommodating all comers. The result was that there was a total registration of 179 different individuals; however, 70 of these were part-time registrants. Enough cannot be said for Dr. Thompson's enthusiasm and his capacity for hard work and fine organization. He telephoned us at all times of the day and night; he telegraphed frequently and wrote scores of letters; he was ably assisted especially by Governor Walter L. Palmer, President Irons and Regent Sloan. The course terminated in a Regional Meeting, which was second to none that had been held in the country. The only question that some have raised is whether or not we should encourage such large classes, although in this particular instance the course was purely didactic, and none suffered, other than from the standpoint of the inability to become intimately acquainted with other members of the class. However, the Chicago Officers attempted to remedy this to a degree by some really extensive entertaining of the group as a whole.

Course No. 6, Special Medicine, at Philadelphia, terminating with a Regional Meeting of this territory yesterday, was, we believe, an excellent course and well received. Dr. McMillan, and his faculty from various Philadelphia Institutions, worked faithfully in an attempt to give the class the best available in Philadelphia at the present time. Instead of holding the class at various institutions, as was done a year ago, with a certain amount of confusion among those unfamiliar with our transportation system, all classes were held at the Philadelphia General Hospital. The registration for this course was not as great as a year ago, but War conditions, including transportation and hotel facilities, interfere more now and, anyhow, it has been observed that the same course, repeated too frequently, does not call forth the same number of registrants each succeeding year. The law of supply and demand is always evident. Some variation in the courses, the institutions and the directors from time to time meets with greater demand than the repetition of the same course too frequently.

From the reports handed to you, you will note that the total registration for the

autumn courses amounted to 447, making a total registration for the year of 854.

### III. Proposed Courses for late winter and spring, 1945:

Course No. 1, *Cardiology*, College of Physicians and Surgeons, Columbia University, New York City, Dr. Robert L. Levy, Director, (March 19-24).

Course No. 2, *Mechanics of Disease*, Harvard University and Peter Bent Brigham Hospital, Dr. George W. Thorn, Director, (April 9-21).

Course No. 3, *Clinical Medicine with Special Emphasis upon the Hematologic Viewpoint*, Ohio State University, Dr. Charles A. Doan, Director, (April 16-21).

Course No. 4, *Gastrointestinal Diseases*, Graduate Hospital, Philadelphia, Dr. Henry L. Bockus, Director, (April 23-28).

Course No. 5, *Applications of Psychiatry to the Practice of Internal Medicine*, University of Wisconsin, Dr. Hans Reese, Director, (April 30-May 5).

The last course has great possibilities of being both practicable and interesting if properly organized and conducted. Much interest in such a course has been expressed by members of the College.

One of our great problems, of course, is being able to organize faculties and obtain facilities under present conditions. I am sure the Advisory Committee on Post-graduate Courses will appreciate such suggestions, instructions or approval as the Board of Regents may be willing to offer.

(President Irons requested the Executive Secretary to present also a report on the regional meetings.)

MR. LOVELAND: For the current calendar year 1944, the following meetings have been held:

1. SOUTHERN CALIFORNIA, at Los Angeles, February 26.
2. MONTANA and WYOMING, at Great Falls, Mont., May 6.
3. MISSISSIPPI, at Jackson, May 9.
4. COLORADO, UTAH, ARIZONA, NEW MEXICO, KANSAS and NEBRASKA, at Denver, June 22-24.
5. IDAHO, OREGON, WASHINGTON, ALBERTA, BRITISH COLUMBIA, MANITOBA and SASKATCHEWAN, at Vancouver, B. C., September 14-15.
6. STATE OF NEW YORK, at New York City, October 20.
7. NEBRASKA and adjacent territory, at Omaha, in conjunction with War-Time Graduate Medical Meetings and the Omaha Mid-West Clinical Society, October 26-27.
8. STATE OF NORTH CAROLINA, at Chapel Hill, November 3.
9. ILLINOIS, INDIANA, IOWA, KENTUCKY, MICHIGAN, MINNESOTA, and WISCONSIN, at Chicago, November 4.
10. WESTERN PENNSYLVANIA, OHIO and WEST VIRGINIA, at Pittsburgh, November 11.
11. EASTERN PENNSYLVANIA, NEW JERSEY and DELAWARE, at Philadelphia, December 15.

Your President, your President-Elect and your Executive Secretary have been in attendance at one or more of the larger and more important of these meetings. Programs have uniformly been of high caliber, and attendance has been gratifying. Especially great enthusiasm was expressed for the meetings at Denver (a three-day meeting in conjunction with War-Time Graduate Medical Meetings), Vancouver (where we obtained the famous Dr. Wassell as one of the guest speakers), and Chi-

ago. Several of these Regional Meetings were the first ones of the character in their territory, such, for instance, as the meeting in Vancouver, the meeting in Denver and the meeting in New York. The meetings, as you already know from copies of programs sent you, have taken many forms, and we have been able to entertain a very large number of Medical Officers from the Armed Forces and a large percentage of our members.

Planned for the immediate future are the following:

1. TENNESSEE, MISSISSIPPI, LOUISIANA, ARKANSAS and EASTERN TEXAS, at Memphis, under Dr. Wm. C. Chaney, Governor for Tennessee, January 25-26, 1945.
2. OKLAHOMA, KANSAS, MISSOURI and WESTERN TEXAS, at Oklahoma City, under Dr. Lea A. Riely, Governor for Oklahoma, February 22-23, 1945.

Under course of organization, or consideration, are Regional Meetings in St. Louis, some city in New England, some city in the Middle Atlantic States and some city in the Southeastern Atlantic States.

The Regional Meeting in St. Louis will be discussed under another item on the Agenda for today, with a view to holding our Annual Business Meeting there in conjunction with the Regional Meeting, similar to the plan we followed last April in Chicago.

We confidently feel that these Regional Meetings continue to make a real contribution during the War, but the membership-at-large, in a great many instances, is looking forward to the time when we shall resume our Annual Sessions.

PRESIDENT IRONS: The report will be received with thanks.

DR. STRONG: I believe the Regional Meeting in Vancouver was a good thing for the American College of Physicians—it was a good opportunity to bring to the attention of the profession in Western Canada the valuable service that this College was rendering. Because of lack of knowledge, there is often a certain lack of interest in the College, and I think meetings of this sort will quickly dispel that lack of knowledge and there will be a tremendous increase in the activities of our College in Western Canada.

DR. BARR: The Vancouver meeting was truly an inspiring meeting and thanks to Dr. Strong's leadership, I feel that the American College of Physicians is launched in a very big way in that district.

PRESIDENT IRONS: The Chicago Regional Meeting and Postgraduate Course were extremely successful. The College is distinctly on the medical map of Chicago.

On resolution by Dr. Stroud, seconded by several and unanimously carried, it was resolved that the Board of Regents convey to the Directors of the Postgraduate Courses and the General Chairman of the Regional Meetings, a vote of thanks and appreciation.

Dr. Frank Borzell, Chairman of the Committee on War-Time Graduate Medical Meetings, reported on the activities of that Committee. In the statistical review of activities, Dr. Borzell recorded that there had been 89 individual meetings, 90 continuation courses, 179 War-Time Graduate Medical Meetings and 831 daily sessions. Meetings had been conducted in 16 civilian institutions, 21 Naval installations and 102 Army installations. The total receipts for the year, \$27,498.43, and the total expenditures (estimated for December), \$24,737.87. Dr. Borzell pointed out the difficulties of preparing a detailed budget for the year 1945, due to uncertainty concerning the continuation of hostilities, but recommended that each contributing organization, the American College of Physicians, American Medical Association and the American College of Surgeons appropriate on the same basis as for 1944. He stated that the Committee on War-Time Graduate Medical Meetings is prepared to

render whatever assistance may be required by the Surgeon's General to augment the teaching personnel at the various military installations for refresher courses planned for medical officers about to be discharged from service.

Dr. Francis Blake, Chairman of the Committee on Fellowships and Awards, reported that all activities of the Committee have been in abeyance during the war by direction of the Board of Regents. Since a year ago, the Committee had received two follow-up reports on publications by Dr. James Hopper, Jr., a former research fellow. While there had been no meeting of the Committee, the Chairman expressed the opinion that it might be advisable to give consideration to renewal of the fellowship program beginning in the autumn of 1945, with sending out notices of fellowships, perhaps in relation to providing opportunities for men returning from the services. Dr. Blake said he would consult other members of the Committee and bring in another report with definite recommendations at the spring meeting of the Board.

Dr. Reginald Fitz, Chairman of the American Board of Internal Medicine, reported that the Board had lost two valuable members during the past year, Dr. Ernest Irons, its former Chairman, and Dr. Frederic M. Hanes, resigned. The Board had examined 633 individuals during the year by written examination, 269 during February and 364 during October. A little over 200 candidates had taken the oral examinations, 57 of whom had been examined by special arrangements outside of the regular meetings, and 54 of these were examined under Colonel William Middleton's guidance in the European Theater of the War. The mortality rate had been about the same as heretofore. Fifteen per cent failed the written examinations and of those taking the oral examinations, about the same percentage of failures occurred, except in the case of men examined in the European Theater, where the percentage of failures was considerably greater. Dr. Fitz reported that 3,526 physicians have been certified, that the number of men considered for certification without examination is being rapidly decreased and that the number of men taking examinations is continuing to grow. The sub-specialty boards were working, on the whole, well, except there are some groups in specialties who have wanted to form their own boards. This is being discouraged. Dr. Fitz said the Board had adequate funds with which to work, both during the present and the future. The Board will require some new appointees by the College in the spring—one to take Dr. Hanes' place, and others to fill vacancies caused by expiring terms. It was further pointed out that the Board would desire to know the time and place of the annual meeting of the College in the spring of 1945, so that oral examinations could be arranged and scheduled.

There followed a discussion of the method of additional certification in the sub-specialties. It was explained by various members of the American Board that all candidates must pass the regular written examination and part of the regular oral examination, following which they may be admitted to the special examinations in the sub-specialties.

Dr. James E. Paullin, Acting Chairman of the Committee on Public Relations, presented the following resignations which were accepted:

- Lt. Col. John B. Grow, (MC), USA, (Associate).
- Dr. Virginia Hale (Associate), Gales Ferry, Conn.
- Dr. Claire E. Healey (Associate), Elgin, Ill.
- Dr. George H. Hess, F.A.C.P., Uniontown, Pa.

Dr. Herbert A. Burns, F.A.C.P., Minneapolis, Minn., was discontinued on the Roster, and Dr. Clayton E. Royce, F.A.C.P., Jacksonville, Fla., was accorded waiver of dues because of ill health and retirement from practice.

DR. PAULLIN (Continuing his report): The Committee received a lengthy series of resolutions from the Illinois State Medical Society concerning the support of the Miller Bill, which was introduced in Congress and which had to do with the de-

ferment of qualified pre-medical students over the age of 18, in order that the quota of medical students in our colleges could be maintained after the year 1945. Only about 60 per cent of the students in schools will be in the V-3 or V-12 program after 1945, and that will leave 40 per cent of vacancies in most schools. The Miller Bill is an effort to get Selective Service to defer approximately 6,000 men a year for the study of medicine. This has been taken up very actively by the American Medical Association, the Council on Medical Education and Hospitals and various other organizations. Your Committee thinks it would meet with a sufficient amount of action if the Board of Regents approve the resolution. I so move.

DR. STRONG: I second the motion.

GENERAL MORGAN: I have no very firm convictions about this. I have not heard of the Miller Bill before, but I question the advisability of our College going into matters that have to do with governmental policy. It probably would be a mistake, in my opinion, for this College to project itself into things concerning organized medicine of that type. The American Medical Association and the State Societies give an outlet for expression, and I doubt if the College, by and large, should enter into a matter of this kind. I think the College would do well to stick to professional matters.

DR. SLOAN: I am inclined to think that we should act as individuals rather than as a College.

DR. PAULLIN: It is only a question of providing students for the study of medicine and care of the civilian population. The Army and Navy have as many doctors as they need, and the poor civilians have very few and no chance of getting more after 1948. Practically every other organization has approved this Bill and it is more or less immaterial whether the College does or not.

GENERAL MORGAN: I might just elaborate on what I was thinking. I believe the strength of the College lies in its manifest mission of doing all that it can do to elevate the standards of the practice of medicine. Those organizations that stick to their knitting get along, by and large, better than those that let themselves be drawn into other things.

(The motion was put to vote and lost by one vote.)

DR. PAULLIN: Your Committee has a communication from Dr. Chauncey D. Leake, Vice President and Dean of the University of Texas. He requests that this College become interested in promoting and maintaining the best possible standards for hospital pharmacies; that pharmacies in hospitals should have a capable pharmacist in charge and become a center for chemical consultation throughout the hospital, and might be responsible not only for the manufacture, distribution and dispensing of various drug preparations, but also for solutions, laboratory reagents and sterile supplies. The Committee expresses sympathy with Dr. Leake's point of view, but feels that this is not within the province of the College and moves that this recommendation be adopted.

(The motion was seconded and unanimously carried.)

DR. PAULLIN: We shall refer an inquiry from a Richmond, Va., physician concerning obstetrical privileges granted doctors at a local hospital, to the American College of Surgeons.

Dr. Walter W. Palmer, Chairman of the Committee on Post-War Planning for Medical Service, reported that the Central Committee had several meetings since the last meeting of the Board of Regents and that proceedings of these meetings have been reported in the Journal of the American Medical Association. The chief items of interest had been reports from time to time by Colonel Harold C. Lueth, Liaison Officer of the Surgeon General's Office with the Council on Medical Education and Hospitals. A questionnaire was sent to every man in the service, Army, Navy and Public Health Service, asking what he would like to do after the war

and what training he desired. 20,000 replies have been received and classified; younger men want more resident work and longer training; older men want more refresher courses. In the resident and special training group, surgeons by far outweigh all others; internal medicine is second; obstetrics and gynecology is third. Requests for long-term training in surgery are going to be far beyond the facilities this country is able to supply. Another questionnaire is being prepared to determine the possibility of increasing the facilities of the country for internships, residencies and other special training. The previous calculation has been that most worthy men could be accommodated, if present opportunities could be doubled and if demobilization takes place not too rapidly. Dr. Palmer also reported that the Committee has been compiling lists from medical schools of essential teachers, key men, that they desire to have released early from military duty. This particular work is being done through the Association of American Medical Colleges. 53 schools have reported the names of 403 from the Army and 109 from the Navy, which is 8 per cent of medical officers in the Army and 2 per cent of those in the Navy. The list will be passed through the Office of Procurement and Assignment, and the Committee will collaborate with that agency.

Dr. Palmer reported also that a sub-committee of the Committee on Post-War Planning, consisting of Father Schwitalla, Dr. Frederick Collier and himself, had spent a day visiting the Veterans Administration to study the possibilities of organizing residencies of a caliber suitable for postgraduate work. Clinical material is ample, but the possibility of organizing anything that would be acceptable is still uncertain. A conference had also been held in Washington with Mr. Harold V. Sterling, who will probably administer the GI Bill. It is apparent that the Bill will be interpreted broadly with every effort to help every man coming out of the Service. Medical men will be able to get subsistence at the rate of \$50.00 per month if single, \$75.00 per month if married, and \$500.00 per school year for training. Hospitals will probably be acceptable institutions of training.

Dr. Palmer stated that the Committee had also explored war surpluses and their post-war distribution. The National Research Council's Committee on Essential Drugs and Medical Supplies, of which Dr. Palmer is Chairman, made certain recommendations to the Senate Committee before the law was passed.

Dr. Palmer said another item considered by the Committee is a recommendation concerning the granting of temporary licenses by State Boards. The Committee has approved of such recommendation, but because it was not restricted to men in Service, as they were demobilized, several objections had been raised by various medical boards, with the result that the Committee recommended modification, restricting the granting of temporary licenses to men in Service or to men as they get out of Service, providing State Boards agree.

Dr. O. H. Perry Pepper presented the report on the Committee on Finance, making the following points:

The income of the College exceeded expectations by approximately \$20,000.00, chiefly due to increase in Life Memberships. The surplus for the year 1944 will be about \$25,000.00, \$22,000.00 of which is not available for use, being represented by Life Membership fees which are deposited in the Endowment Fund. The College operated during 1944 well within its budget; the Committee had reviewed budgets for 1945, showing total estimated income of \$103,000.00 and expenditures of \$89,270.00, leaving an anticipated surplus of \$13,830.00.

By resolution, the proposed budgets for 1945 were approved, with certain minor additions for special purposes. Also by resolution, the following matters affecting finances were acted upon:



The suggestion from the American Physicians Art Association that the College offer prizes for the stimulation of painting of medical subjects, be politely declined; that the College contribute \$5,000.00 toward the program of the War-Time Graduate Medical Meetings during 1945; that the College authorize completion of all necessary arrangements for the establishment and initiation as of January 1, 1945, of a pension system for full-time employees, in accordance with principles adopted at the preceding meeting of the Board, and that the Secretary General, Treasurer and Chairman of the Finance Committee constitute the Pension Committee, the Secretary General acting as Trustee.

Full and detailed statements of receipts and expenditures of the College for 1944, with estimates for November and December, as well as the detailed budgets proposed for 1945, were presented to the Regents for review, and were subsequently approved.

In closing his report, which was adopted as a whole, Dr. Pepper re-affirmed the Committee's satisfaction with the services of Drexel & Company, the financial counsel of the College, and on behalf of the Committee expressed appreciation of the efficiency of the Executive Secretary in all matters.

Dr. William D. Stroud, Treasurer, presented the following report:

"I am gratified to report that the financial condition of the College is excellent; that the income for 1944 will be approximately \$20,000.00 in excess of that anticipated a year ago; that the College has operated within its budget for the current year; that the accounts of the College will be audited by a professional accountant at the end of the year. A more detailed report is not presented now because the Executive Secretary has already placed in your hands the analysis of income and expenditures for the year, and the Chairman of the Finance Committee has made an all-inclusive report. At the last meeting of the Board, we appropriated up to \$1,000.00 to the National Council for the Prevention and Treatment of Rheumatic Fever. To date, the Council has not called for this amount. This is because the Council is attempting to raise a total of \$100,000.00 before it begins its work.

"The market value of the investments of the College is \$295,868.00, of which 47.3 per cent is in Bonds, 22.4 per cent in Preferred Stock and 27.7 per cent in Common Stocks. The cash income from these investments for the last year has been \$10,781.00, a yield of 3.74 per cent."

Dr. Stroud, as Chairman of the House Committee, thereafter presented a report on the upkeep, maintenance and improvement of the Headquarters building and grounds, with a total expenditure of \$6,092.03. The College continues to house the War-time Graduate Medical Meetings, furnishing them without charge room, heat, light and service.

Dr. Chauncey W. Dowden, Chairman of the Board of Governors, reported at length on the interim activities of that Board and read several letters from Governors concerning policies of the College. Several Governors had discussed the matter of making certification a prerequisite for Associateship, and the general attitude appeared to be unsatisfactory. Among the letters read was one from Surgeon General Thomas Parran, advocating recognition of competence in medicine in the Service as requisites for membership in the College, rather than the extension of certifying examinations.

At this point, the Board took up the consideration of holding an Annual Business Meeting and brief war session in the spring. By resolution, it was decided that these meetings be conducted in St. Louis, in connection with the Regional, War-Time Meeting under the general chairmanship of Dr. Ralph Kinsella, Governor for Missouri. It was suggested that the Regional, War-Time Meeting consist of one day of clinics

and one day of formal papers, that medical officers of the Armed Forces be invited and that one day be devoted to a combined executive session of the Board of Governors and Board of Regents, to the Annual Business Meeting for the transaction of formal business of the College and the election of Officers, Regents and Governors. Dr. Kinsella was appointed Chairman of Local Arrangements.

Subsequently, the dates of May 3-4 were selected for the scientific aspects of the meeting, and May 5 for the executive session of the Regents and Governors and the Annual Business Meeting.

The Committee on Credentials was authorized to hold a meeting about three weeks in advance of the annual meeting to review the credentials of candidates for membership.

*Adjournment*